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THE MEDICAL CLINICS OF NORTH AMERICA

Volume 7

Number 4

CLINIC OF DR RALPH H MAJOR

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EMPHYEMA TREATED WITH GENTIAN VIOLET

THIS patient has had an extremely stormy time. There was a great deal of doubt for days as to whether she would recover. I feel that the greatest single factor in her recovery has been a therapeutic procedure, which will be described later.

The patient is a white woman aged twenty-seven. She was admitted to the Bell Memorial Hospital with a cough, pain in left side of the chest, and weakness.

Family History.—Negative.

Personal History.—Patient had diphtheria at ten years and scarlet fever at six years of age. She has had two attacks of pneumonia, one eight years ago and the second one six years ago. The right lung was involved in both attacks.

Present Illness.—Three days before admission the patient had several severe chills with fever, began having a diffused pain over the left side of chest and developed a very irritating cough, with an expectoration which soon became tinged with blood.

Physical Examination.—The patient's temperature on admission was 100° F, respirations 28. She lies on her left side, obviously in pain, and is coughing continually. There is a marked herpes labialis and nasal on the left side. The teeth show very marked caries. Examination of chest shows the movement is limited on the left side. Over this side the percussion note is somewhat impaired and there are numerous

fine moist râles The heart is negative The abdomen shows nothing abnormal

Laboratory Findings.—The urine is normal The blood examination shows R B C 3,168,000, W B C 13,500, hemoglobin 65 per cent The differential count shows 75 per cent neutrophils The blood Wassermann is negative This patient at the time of admission presented the typical picture of an early lobar pneumonia During the next few days there was a gradual increase in the temperature and pulse-rate and the white blood-count three days later had risen to 28,850 The blood-culture was negative and the sputum culture showed a pure culture of *Streptococcus hemolyticus*

Two days after admission the patient developed a loud friction-rub in the left axilla, and two days later she had very definite signs of fluid, the percussion note being quite flat and the breath signs being absent over the left side of the chest An x-ray of the chest showed a dense shadow over the entire left side of the chest, with a displacement of the heart to the right (Fig 172) A needle was inserted into the left side of the chest and a purulent fluid obtained Cultures were made of this fluid and the *Streptococcus hemolyticus* was obtained in pure culture

The patient's condition at this time was desperate The temperature varied from 101° to 101.2° F, the pulse-rate varied from 120 to 160 per minute The patient obviously had a streptococcus empyema, but operation in her condition was quite out of the question Instead of operating, the chest was aspirated with the needle, 1000 c c of pus was removed, and 100 c c of an aqueous solution of gentian violet, 1:1000, was injected into the left pleural cavity The same procedure was repeated two days later, and again after an interval of two days At the second aspiration 900 c c of fluid was obtained and 100 c c of 1:500 solution of gentian violet injected On the third occasion 750 c c of fluid was obtained and 100 c c of gentian violet, 1:250, injected

The bacteriologic studies of the fluid withdrawn were very interesting Following the first instillation of gentian violet the

number of organisms was remarkably diminished, and following the third instillation the fluid became sterile and has remained so since, although four subsequent aspirations of the chest were



Fig 172

carried out, and a small quantity of fluid recovered on each occasion. The instillations were followed by sharp falls in the patient's temperature (Fig 173), and there was a striking improvement in the patient's condition. At the time the sterile

fluid was obtained the patient's temperature varied from 100° to 101° F, and then gradually came down by lysis to normal, this period, however, lasting about three weeks. The patient's convalescence was greatly prolonged later by the unexpected development of a pneumothorax just a few days before she was planning to leave for her home. This time there was a fresh

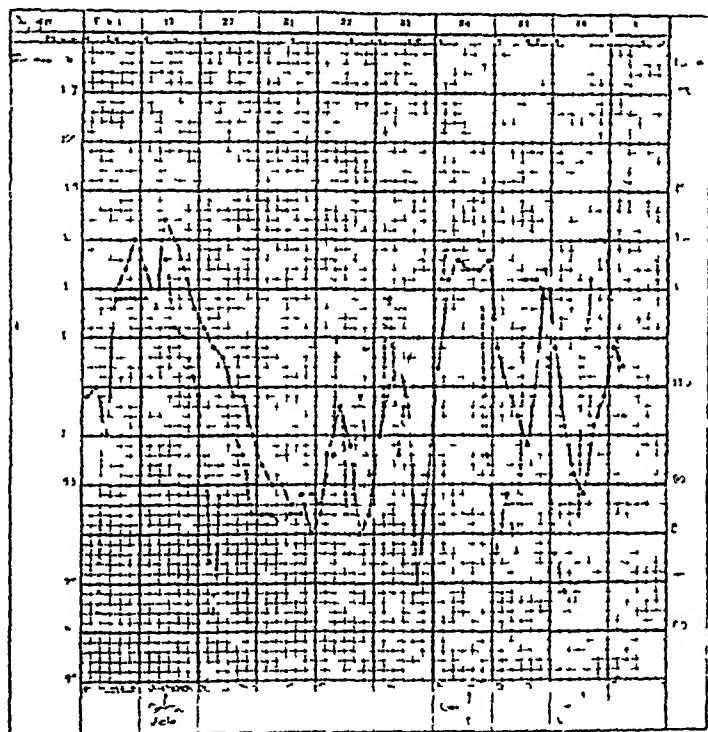


Fig 173 —Chart on temperature and pulse

effusion into the chest which, however, was sterile. At the time the patient was discharged from the hospital all signs of empyema and pneumonia had disappeared, and the collapsed lung, resulting from the pneumothorax, was filling out rapidly.

The effect of the gentian violet in this patient was very striking. Before the World War the dictum generally accepted

was that when you found pus in the chest, operate. The aspiration of pus from the pleural cavity meant a rib resection. We are all familiar with the appalling results which followed such operations during the influenza epidemic in 1917 and 1918. The mortality in some army camps, you recall, was as high as 80 per cent. A further study of this subject taught us that operation was an extremely hazardous procedure at the onset of empyema, and that the patients died after operation not because of their empyema, but because of a coexisting bronchopneumonia. It was subsequently found that the mortality was very much lower if operation upon such patients was delayed.

During the influenza epidemic of 1920 a large number of patients suffering from empyema, mainly of *Streptococcus hemolyticus* origin, were seen. We had learned our lesson in regard to the advantages of delay in operating, and operation was subsequently deferred in these. As I had been for several years interested in the studies of Dr John W. Churchman on the bactericidal action of gentian violet, I thought that it would be interesting to try the effect of this dye in patients suffering from empyema. Theoretically, such a disease should be an excellent one in which to try out such therapy. The disease process here is localized in a cavity which could be partially filled with a non-irritating but highly bactericidal fluid, which could act upon the organisms constantly.

The procedure was tried out in a series of 27 patients, with very encouraging results—51.8 per cent. were cured, 29.6 per cent. came later for operation, 18.5 per cent. died. None of these patients were good surgical risks at the time this treatment was instituted, and the first few patients were given the treatment as a preparation for later operation. The majority of these patients recovered from their empyema and never came to operation. The mortality in the series was due to a coexisting bronchopneumonia and should not be charged against this treatment.

Some of the patients who came later for operation were in much better condition because of this preliminary treatment. One patient especially, I recall, had a bilateral empyema and

was desperately ill for two weeks. Both pleural cavities were treated with gentian violet instillations, and one side healed completely before operation.

The experience of my colleague, Dr. Robert C. Davis, has been even more encouraging than my own. In a series of 18 patients, every patient cleared up under this treatment without operation. The difference in our percentage of recoveries is due partly to the unusual virulence of the *Streptococcus hemolyticus* during the influenza pandemic and because of differences in the bacteriology of the cases, 25 of my patients were due to *Streptococcus hemolyticus*, and only 2 were caused by the pneumococcus, while in Dr. Davis' series about one-half were of streptococcus origin.

The procedure that has been followed is to first aspirate the chest and remove all the pus possible, 100 c c of gentian violet solution is then injected and allowed to remain in the chest. At first it may be advisable to use the solution in a strength of 1:1000, although the second or third instillation, if necessary, may be given in the strength of 1:250. We have seen no evidence that the solutions are irritating. The solutions seem more effective if they are warmed before injection, and should be injected as warm as the patient can take them. There is another patient in our clinic at the present time who has received this treatment. His empyema was due to the pneumococcus, and the fluid became sterile following one instillation.

This treatment obviously has definite limitations. In order to achieve the best results with it the empyema must be diagnosed early and treatment instituted before firm adhesions have formed. It is in this type of patient that we have achieved the most striking results. After dense adhesions and pockets have formed, the problem becomes complicated by a mechanical factor, and unless there is free communication between the various parts of the chest, good results cannot be expected from gentian violet instillation. The dye must come in contact with the infectious material in order to have any effect.

Some critics of this method have maintained that we are not treating empyema because the pus is not thick enough to justify

us in employing this term Our answer is that we do not give the pus in these patients a chance to become very thick

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XANTHOMA DIABETICORUM

WE are all grateful for the discovery of insulin. It has saved many lives, and has made the lot of many a diabetic much easier. The use of it in this clinic has given us an opportunity to see a number of unusual complications in diabetes mellitus. The following patient is one example of them.

This patient is a married man, white, thirty-three years of age, a farmer by occupation. He was admitted to the Bell Memorial Hospital for the treatment of his diabetes.

Family History—The patient's father and mother are living and well. Two brothers and one sister died from diabetes mellitus. Another brother is a diabetic and was recently a patient at this clinic. The patient has 6 sisters, who are living and well. He has one child four years of age, who is also well.

Personal History—The patient has always enjoyed good health. He had measles, mumps, and whooping-cough as a child. The personal history is otherwise quite negative.

Present Illness—The patient's present illness began eighteen months ago, when he noticed that he was drinking large quantities of water and passing a greatly increased amount of urine. These symptoms have persisted since that time, and he has lost between 15 and 20 pounds in weight in spite of a very hearty appetite. Two weeks before admission the patient noticed a rather profuse skin eruption, which appeared on the chest and abdomen and over the extensor surface of the forearms and thighs. This eruption appeared quite suddenly and simultaneously over these areas. It was accompanied by no itching or other disagreeable sensation.

Physical Examination—The physical examination is essentially negative except for the skin eruption. This eruption consists of small yellowish-orange nodules, quite firm and discrete, varying in diameter from 0.5 to 2 mm. None of the nodules are confluent and they do not show any tendency to scale (Fig. 174). The lungs are clear on percussion and auscultation.

The heart is of normal size and the sounds are clear The blood-pressure is 105 systolic and 80 diastolic



Fig 174

A single specimen of urine on admission showed a very heavy tract of sugar, with diacetic acid and acetone A quanti-

tative determination of the sugar showed that the patient had excreted 30 grams of sugar in the first twenty-four hours after admission to the hospital. The patient's fasting blood-sugar on admission was 278 mg per 100 c c and the carbon dioxide tension was 18 volumes per cent (Van Slyke). When the patient's blood was allowed to remain in a test-tube the red cells sank to the bottom, leaving above a very thick, creamy looking serum. This appearance is characteristic of lipemia, and a drop of the patient's blood-serum when stained with sudan III showed an enormous number of globules which stained red. The patient's blood cholesterol was 386 mg per 100 c c.

This patient gives a history of considerable interest because of the high incidence of diabetes mellitus in his generation. He is a member of a family of 12 children, 5 of whom have had diabetes, 3 dying of the disease.

The skin complication that he presents is a typical picture of xanthoma diabeticorum. This disease is described by Sutton as "exceedingly rare," and most other authorities refer to it as a rare complication of diabetes. Insulin is bringing more patients to hospitals, and with these patients we are seeing more unusual complications than we used to see.

During the past five months I have seen 4 diabetics with xanthoma diabeticorum. Norman Walker in 1897 stated that only 30 cases of xanthoma diabeticorum had been reported up to that time. I have recently gone over the literature and found records of 74 cases, not including the 4 that have been under my care.

The disease was first described by Addison and Gull in 1850. Every one interested in this disease should read their article in Guy's Hospital Reports. Their description of the lesions, which still remains unsurpassed, is so clear and vivid that anyone reading it should be able to diagnose his first case of xanthoma diabeticorum.

This condition is produced by a deposit of cholesterol, fat, and lipid bodies beneath the skin. It is probable that most or all of these patients have a lipemia and hypercholesterolemia. The 4 patients studied in this clinic all showed lipemia and a

high blood cholesterol Griffith, Mook and Weiss, and Nicholson have also called attention to the high blood cholesterol in these patients

The microscopic appearance of these nodules is often at first glance rather disappointing (Fig 175) The sections show a very marked fibrosis with many clear xanthoma cells When this tissue is stained, however, by special fat stains the picture is very striking The special stains show the presence of large amounts of neutral fat, lipoid bodies, and cholesterol

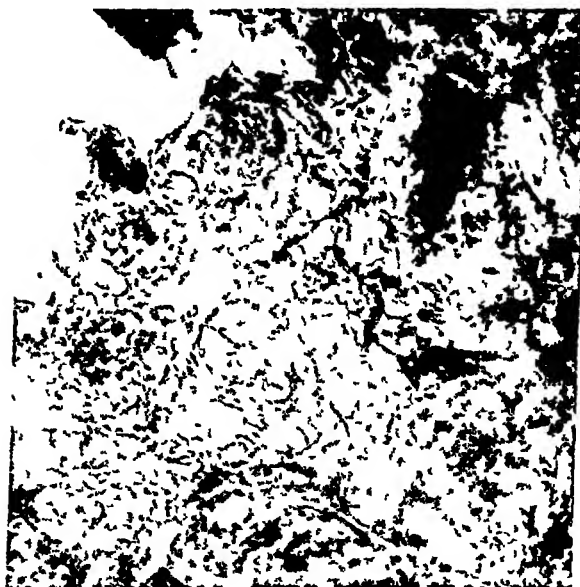


Fig 175

Balzer and Marie drew a very interesting contrast in the appearance of the skin lesions in a patient whom they observed They described "elements miliaires" and "elements lenticulaires," and noted that while the former cleared up rapidly when the patient's urine became sugar free, the latter often proved resistant to treatment Since our patient presents mainly the "elements miliaires" the results of treatment here should be, I think very good

The older authors in their case reports of xanthoma diabeticorum often expressed amazement because in some patients the skin lesions were worse when the patient became aglycosuric, while in other patients the skin lesions improved in spite of the fact that the patient continued to show sugar in his urine. Such an experience should not surprise us. Xanthoma diabeticorum is due primarily to a disturbance in the fat metabolism, and while it is not entirely independent of disturbances in the carbohydrate metabolism, yet it may show a certain independence at times.

There has been much discussion in the past about the importance of trauma in the production of these lesions. Many observers have called attention to the tendency of these lesions to be more marked on the knees, elbows, and other parts of the body which are most subject to rubbing or slight traumata. Other students of this disease have minimized such factors and laid stress entirely upon the abnormal fat chemistry.

Both factors are of importance. Without an abnormal fat metabolism there will be no deposit of fat lipoids and cholesterol beneath the skin. On the other hand, a very slight trauma may determine the location of such a deposit. I have described elsewhere a diabetic patient who developed a single xanthoma lesion on the site of a healing mosquito bite.

The rapidity with which these lesions clear up depends partly upon the size of the papules and partly upon their blood-supply. If the lesions are small and their blood-supply good, they are absorbed rapidly under treatment. When the papules, however, are large, confluent, and have a very scant blood-supply they disappear very slowly.

Later—This patient, following three weeks of dietary measures and insulin therapy, was again seen, and the skin eruption had entirely disappeared. The only signs of it persisting was a small number of brownish discolorations marking the old site of the papules. The patient's blood-sugar at this time was 115 mg per 100 c.c. and the blood cholesterol was 170 mg per 100 c.c. His urine had shown no sugar for eighteen days.

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HYPERTHYROIDISM ASSOCIATED WITH ACIDOSIS

THE following patient illustrates a complication of thyroid disease which is probably quite common. Since my attention was first directed to these patients I have become convinced that this complication, always distressing and often fatal, is rather frequent. The patient is a colored woman aged forty-nine, who was admitted to the Bell Memorial Hospital complaining of nervousness, weakness, and loss of weight.

Family History—Negative. No history of any similar illness in the family.

Personal History—The patient has had frequent sore throats, has suffered from frequent toothaches, and has had a number of teeth extracted.

Present Illness—The patient suffered from her present illness for three years before admission to the hospital. Three years ago she was frightened by another woman, who stepped up suddenly behind her. The patient thought she was going to be attacked and possibly killed. She was very much frightened, screamed loudly, and was almost unable to walk because of exhaustion. She remained in bed for three days, and at the end of that time was removed to a hospital, where she was told that she had a tumor in her neck. During the past year the nervousness has become more marked, she has felt very weak, and has lost 20 pounds in weight.

Physical Examination—The patient is a small and poorly nourished woman, with a warm, moist skin, and she has a very alert mental attitude and an anxious expression. She looks very much as she must have looked three years ago when she was frightened. This patient's anxious, fearful expression is described very well by the term "crystallized terror," used by Loebius (Fig 176). The eyes show a marked exophthalmos, a positive von Graefe sign, and converge very poorly.

The tongue is clean, somewhat tremulous, and the teeth are in very bad condition, showing marked pyorrhea and caries.

Palpation of the neck shows enlarged anterior and posterior cervical lymph-glands. The thyroid is diffusely enlarged, although the degree of enlargement is not marked. There is a slight thrill felt over the left lobe of the thyroid and a loud systolic bruit is also heard. Both carotids show a marked pulsation. The lungs are clear and the heart is negative except for a soft systolic murmur, which is poorly transmitted. There is a marked retrosternal dullness 4.5 cm. to the right and 3.5



Fig. 176—Hyperthyroidism associated with acidosis

cm. to the left of the midsternal line. The pulse-rate is 120 per minute, the blood-pressure is 160 systolic and 110 diastolic. The radial artery shows a diffuse thickening. There is a fine tremor of the fingers, the rate varying from five to six movements per second.

The history of this patient, with the results of the physical examination, stamp her as an example of hyperthyroidism. The history of nervousness and loss of weight is very suggestive

The onset, after a severe fright, is also very interesting. Many patients suffering from Graves' disease date the onset of their illness from fright.

The physical examination of this patient shows that the major symptoms of Graves' disease—exophthalmos, struma, tachycardia, and fine tremor—are all present.

This patient presents a moderate arterial hypertension, which is so common in Graves' disease, and also shows an increased area of dulness behind the manubrium. Such an area of dulness may be due to an enlarged thymus, which is frequently found in Graves' disease. It is more probable, however, that we are dealing here with dilatation of the aorta, associated with the arteriosclerosis and the arterial hypertension.

Laboratory examinations show that the urine is negative except for an occasional trace of albumin. The blood examination shows R B C 5,160,000, W B C 12,800, hemoglobin 90 per cent. A differential count shows 71 per cent neutrophils, 23 per cent small lymphocytes, and 6 per cent large lymphocytes. Studies of the blood, non-protein, nitrogen, urea, sugar, chlorids, creatinin, and carbon dioxide tension all present normal values. The basal metabolic test, on the day after admission, showed a rate of 53 per cent plus. The x-ray examination of chest showed a broad mediastinal shadow, which upon further examination proved to be due to a dilated aorta. This patient was seen by Dr M T Sudler, and it was decided to ligate the superior thyroid artery after preliminary treatment for several weeks.

Under rest in bed the patient's condition gradually improved, until about two weeks after admission, when one day the patient's pulse suddenly rose from 90 to 120, and at times was as rapid as 160 per minute. At the same time there was an elevation of temperature to 100° F, the patient became somewhat irrational, excessively nervous, and appeared quite toxic.

Examination of the blood showed a carbon dioxide tension of 20 volumes per cent (Van Slyke), and the urine showed the presence of diacetic acid and acetone. The patient was immediately started out on large doses of sodium bicarbonate,

receiving 3 grams every two hours for ten doses, and was also given 1000 c c of 5 per cent glucose solution by rectum. The changes in the patient's condition that followed this therapy were very striking. Within eight hours the patient's general appearance was markedly improved and she appeared much less toxic. During the next twenty-four hours the patient's carbon dioxide tension rose to 40 volumes per cent and the diacetic acid and acetone disappeared from the urine. A few days later the left superior thyroid artery was ligated and the patient left the hospital very much improved.

I have been very much interested in the question of acidosis in hyperthyroidism, and have recently recorded some experiences with it. It is difficult to say just how common it is. Before operation it probably does not occur very frequently, while after operation it is extremely common.

The patients in our clinic who have shown an acidosis complicating hyperthyroidism have responded very promptly to alkaline therapy. Fortunately, none of these, however, have been examples of the most severe type of thyrotoxicosis. I feel convinced, however, that it is a complication of hyperthyroidism that is frequently overlooked and at times overlooked with disastrous results. The profound effect of the thyroid gland upon the metabolism is well known. Disturbances of the carbohydrate, fat, and protein metabolism have been described in thyroid disease. Such metabolic disturbances probably produce an acidosis very frequently.

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CLINIC OF DR. PETER T BOHAN

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A CASE OF LIGNEOUS THYROIDITIS ASSOCIATED WITH HIGH-GRADE DENTAL INFECTION

THIS case was referred to me by Dr Axford, of Leavenworth, Kansas, and was admitted to Bell Memorial Hospital May 5, 1923. She is a married woman, thirty-eight years old, and the mother of 4 living children. Her family history is negative, none of her relatives ever had goiter. Her menstrual history is normal, the last period two weeks before admission. She never had rheumatism or any illness of importance except pneumonia in childhood. She never had a goiter.

On admission to the hospital she was complaining of a cough, dyspnea, a painful swelling of the neck, nervousness, and a loss of weight.

Her present trouble began in January, four months before admission, with a swelling of the neck that has increased in size during the past month and has become quite tender. In February she began to have spells of coughing that are increasing in frequency and are accompanied by a sense of suffocation. These spells last from ten to twenty minutes and come on every six to eight hours. For three or four weeks there has been some difficulty in breathing, so that the patient sleeps propped up in bed. There has been no dysphagia. For over two months the temperature has ranged from 99° to 100.5° F. Since January there has been a loss of 30 pounds in weight.

Physical Examination —The patient was found sitting up in bed, quite alert mentally, slightly nervous, a good color, but there was a definite though not marked inspiratory dyspnea. The temperature was 100.5° F, pulse, 104, slight tremor. The eyes were negative. There was marked oral sepsis, tonsils apparently diseased. There was swelling with marked indura-

tion of the tissues of the neck on both sides in the region of the thyroid gland. A lump could be made out on the left side that seemed to be the left lobe of the thyroid. This did not move on swallowing, which caused the patient some discomfort. The whole swollen area was quite tender and was truly as hard as wood. The induration and stiffness of the involved tissues limited the motions of the head in all directions. The skin was not red. There were no palpable glands. No abnormal dullness over the upper sternum could be made out on percussion. The lungs were negative except for prolonged inspiratory murmur on both sides. The rest of the physical examination revealed nothing abnormal. The urine was negative.

The blood examination showed hemoglobin 90 per cent, red cells 4,800,000, leukocytes 14,200. The Wassermann test was negative.

Skiagraph of the chest showed a shadow superimposed on the spinal column in the region of the first, second, and third dorsal vertebræ. The trachea was deflected to the left and apparently compressed. The hilus shadows were slightly accentuated, but the chest was otherwise negative. Films of the teeth showed 11 with apical infection and all teeth showed pyorrhea in varying degrees.

The metabolic rate was +26.

The diagnosis rested between malignancy of the thyroid and acute thyroiditis. Although the temperature, leukocytosis, and tenderness strongly suggested an inflammatory condition, on account of the lack of redness of the skin or fluctuation, and the extensive induration and marked density of the tissues with pressure symptoms, a tentative diagnosis of malignancy was made. She was given three x-ray treatments with apparent benefit.

The medication consisted of 5 drops of saturated solution of sodium iodid three times a day, and codein and bromids as needed for pain or restlessness.

Her condition grew steadily worse, and on May 17th, twelve days after admission, there was high-grade cyanosis of the face and extremities. The dyspnea was marked and the crowing

inspiration could be heard several feet away Dr Merwin T. Sudler was called in consultation and some operative procedure to relieve the rapidly developing asphyxiation was decided upon Under gas-oxygen anesthesia the isthmus of the thyroid was cut and a mass approximately $2\frac{1}{2}$ inches long and 2 inches wide comprising the right lobe was removed The cavity from which the mass was removed was lined with dense, white fibrous tissue The trachea was embedded in similar tissue, com-

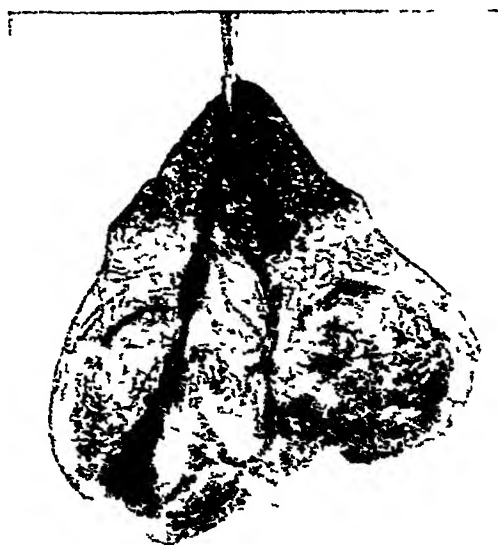


Fig 177—Lobe of thyroid opened up to show appearance of the cross-section

pressed, and pushed to the left As this mass was lifted from the trachea the distressing noise with each inspiration disappeared and the color of the skin returned to normal For two days she was free from dyspnea, but the difficult breathing and cough returned By July 7th she was almost as bad as before, so that Dr Sudler attempted to relieve her by removing some of the dense tissue from the trachea, but was unsuccessful, and Dr L P Hall was asked to do a tracheotomy to prevent an imminent asphyxiation With the tracheotomy tube she

was fairly comfortable except for the distressing spells of coughing

The mass, when removed, was about the size of a hen's egg, smooth, and as hard as wood. It cut with increased resistance, and the cut surface showed a mottled gray and opaque, white color. A small amount of fairly normal appearing thyroid tissue could be seen.



Fig. 178 —Microphoto, raph—through dense opaque area in lobe showing nothing but the difference between sclerosis and chronic inflammatory reaction

Pathologic Report by Dr. H. R. Wahl—Section through the apparently normal thyroid tissue shows the follicles filled with colloid, and there is a diffuse fibrosis. Sections through other portions of the mass show hyaline fibrous tissue, round-cell infiltration, and areas of chronic inflammatory reaction in which there are nests of thyroid follicles. There is no definite caseation. There is nothing upon which one could justify a suspicion of tuberculosis, syphilis, or malignancy.

Diagnosis—Chronic thyroiditis with extensive fibrous encapsulation

On June 30th three abscessed teeth were extracted, and the cultures made from these by Dr R. L. Haden showed colonies of a green-producing streptococcus and staphylococcus. On July 2d two rabbits were injected intravenously with 5 c c of this culture, one of the animals died during the night and the other was killed two days later. Autopsy of the rabbits showed that both had extensive hemorrhages in the thyroid gland and marked edema and small hemorrhages in the thymus, which was about four times the normal size. No other lesions were found.

On account of the heat the patient was discharged from the hospital July 14th. There had been considerable improvement in her general health. The neck was less swollen and not so tender and the tissues were perceptibly softer.

She returned to the hospital September 1st, still wearing the tracheotomy tube, but much improved in every way. There had been a gain of 15 pounds in weight, temperature and pulse were normal. The swelling of the neck had completely disappeared and the induration of the tissues had almost disappeared.

Remarks—In this patient the clinical course of the disease and the microscopic examination of the gland seem to justify the diagnosis of ligneous thyroiditis, an affection of the thyroid first described by Riedel in 1896 as "eisenharte strumitis"—iron-hard strumitis. It was christened by Delore "La thyroidite ligneuse," "ligneous thyroiditis," the name usually given it.

In this case, as in most of the reported cases, malignancy of the thyroid, on account of the density of the tissues, was suspected at first, but a probable diagnosis of thyroiditis was made before the operation. The most important point in differentiating this condition of the thyroid from malignancy is that the thing does not look nor feel just like a malignant process. There is comparatively early involvement of all the tissues in the neck, not only both lobes of the thyroid, but the trachea, muscles, nerves, and blood-vessels, and the limits of the infiltration are not well defined. Because both lobes of the

thyroid are involved the trachea is usually compressed and dyspnea occurs early. Tracheal obstruction is the most dangerous feature of the disease. Dysphagia, a common symptom in malignancy, is either absent or not marked. The course of the disease is three to four months or longer. Most of the reported cases have recovered, a few without any treatment, a few following x-ray treatments, and others after surgical removal of the dense tissue around the trachea and part of the thyroid. Removal of the whole thyroid is impossible and not necessary. If asphyxiation seems imminent, tracheotomy should be done.

The etiology of this form of thyroiditis seems to be obscure. Such concomitant conditions as syphilis, tuberculosis, and the infectious diseases have been recognized. It is possible that all cases are not due to the same cause. In this patient oral sepsis would seem to be the etiologic factor as indicated by the involvement of the thyroid and the thymus in the rabbits injected with cultures from the infected teeth. If the relation of focal infection to the condition had been recognized earlier and the infected teeth extracted, operative procedure on the thyroid might have been avoided.

From a study of this case, as well as from a review of the literature, I would epitomize the important features of this rare affection as follows:

- 1 Enlargement of both lobes of the thyroid
- 2 The tissues on the anterior surface of the neck are indurated and feel as hard as iron
- 3 Tenderness
- 4 No fluctuation
- 5 Fever
- 6 Slight leukocytosis
- 7 Dyspnea early, but no dysphagia
- 8 Course, three or four months
- 9 No relief obtained from application of ice or from iodids
- 10 x-Ray claimed to be specific in some cases
- 11 Remove foci of infection. If necessary operate to relieve pressure symptoms

TWO CASES OF HEMIPLEGIA, WITH RECOVERY, PROBABLY DUE TO INFECTION IN THE NASAL ACCESSORY SINUSES

SUCH intracranial complications of infection in the accessory sinuses of the nose as purulent meningitis, brain abscess, encephalitis, or sinus thrombosis are not uncommon and are fairly well understood. That a patient with chronic infection of these sinuses may develop some intracranial condition and recover seems not to be generally recognized. Brain and meningeal complications of infections in the paranasal sinuses are similar to such complications in infection in the middle ear and the mastoid cells. The routes of infection are analogous, such as necrosis of the bone through the lymphatics, venous thrombosis, etc. In inflammation near the meninges, as in the middle ear or in the accessory sinuses, changes in the meninges occur that may not develop beyond the stage of edema and congestion. The intimate anatomic relationship existing between the accessory sinuses of the nose and the meninges indicates the danger of intracranial complications when a nasal sinusitis exists.

The average thickness of the bone between the optic foramen and the sphenoidal sinus is 0.5 mm, and in some instances 0.2 mm only (Schaeffer). Infection occasionally extends from the sphenoidal sinus through this thin partition of bone and causes optic neuritis.

Congenital or pathologic defects in the cerebral wall of the frontal sinus have been found where the only barrier between infection in the sinus and the dura was mucous membrane.

Infection of the dura from neighborhood infection, such as paranasal sinusitis or mastoiditis, does not always cause brain abscess, suppurative leptomeningitis, or subdural abscess, but, like infection of the pleura or pericardium, the result may be and frequently is a circumscribed fibrinous exudate.

Indeed, pachymeningitis externa has been caused by infection extending through an intact skull as in erysipelas of the scalp and in infected scalp wounds. Infection of the accessory sinuses as a possible etiologic factor in pachymeningitis interna hemorrhagica is indicated in one of the cases of this disease reported by Dunn.

Pachymeningitis externa is usually localized and the symptoms may be general or focal. A good example of the symptomatology are the symptoms that may occur a few days or a few weeks after an injury to the head. The spinal fluid in this condition will be negative unless there is some involvement of the inner layer of the dura. In these 2 cases the spinal fluid was normal, but the spinal puncture was not done until after the patients recovered from the paralysis—four weeks in one case and five months in the other.

The probable diagnosis of pachymeningitis externa caused by the neighborhood infection in the accessory sinuses is based solely on the clinical evidence. The usual brain complications of such infections as abscess or encephalitis are much less likely to speedily recover.

Case I—Miss D, single, twenty-four years old, was admitted to Bell Memorial Hospital February 21, 1923. Her first admission to this hospital was March 30, 1921. The history obtained at that time is as follows. School-teacher, twenty-two years of age. Menstrual history normal. Father, mother, and a sister living and well. No brothers or sisters dead. No family history of asthma or of "hives." She has had no past illnesses except the diseases of childhood and pneumonia in April, 1915. She had a tonsillectomy in November, 1915, and a nasal operation in the fall of 1920.

Her complaints on her first admission in 1921 consisted of asthma, "hives," diarrhea, and headaches. Her trouble began in the fall of 1915 with asthma which lasted four weeks. As this subsided she began to have abdominal cramps and diarrhea, having six to ten watery, mucous stools a day. This intestinal condition lasted about three weeks, and during this time she

suffered almost continuously from hives. The following three months she was free from symptoms. She then developed another attack of asthma, lasting three weeks, followed by diarrhea and hives. From 1915 to 1920, every three or four months, she would have an attack of asthma, followed by diarrhea and hives. For over a year she has suffered almost continuously from asthma and hives, but the spells of diarrhea have been less frequent and of shorter duration. She spent the fall of 1916 in Oregon and the summer of 1917 in Colorado, without any relief of symptoms. During the summer of 1919 she had a "bad cold in her head," and since then has had a severe headache nearly every morning, which would disappear in a few hours. At times the pain was so intense that it caused vomiting.

One night in November, 1920, after the headaches had been unusually severe for a few weeks, while sitting up in bed she noticed a "drawing" of the right leg and arm, and in a few minutes lost consciousness. On regaining consciousness, about an hour later, she could not speak and was paralyzed on the right side of the body. In the following ten hours she had five convulsions. She regained her speech in four or five days and the use of her arm and leg in about a month. Her physicians diagnosed syphilis of the brain, a diagnosis that is too often made in obscure brain lesions.

The important features of her findings on her first admission to the hospital, three months after the hemiplegia came on, are as follows:

A roentgenogram of the head showed all the nasal sinuses cloudy. No evidence of the hemiplegia was found except increased knee reflex on the right side, and a slight but definite Babinski reflex on the right foot. The lungs were moderately emphysematous and there were numerous dry râles. The physical examination of the rest of the body revealed nothing abnormal. The eyes, ears, mouth, and heart were negative. The temperature was normal, pulse 68, and blood-pressure 90 over 65.

Examination of the blood showed hemoglobin 85 per cent,

red cells 4,200,000, leukocytes 14,500 The differential count of the leukocytes showed polymorphonuclears 46 per cent, lymphocytes 20 per cent, transitionals 2 per cent, and eosinophils 32 per cent In six blood examinations the eosinophils ranged between 28 and 37 per cent In eighteen stool examinations no parasites or ova were found The blood Wassermann was negative The spinal fluid was clear, 6 cells to the cubic centimeter, and the Wassermann, globulin, and Lange's gold test were all negative

She was referred to Dr E P Hall, who reported his findings as follows "Infection of both maxillary and both frontal sinuses Suppurative ethmoiditis and sphenoiditis and nasal polypi On February 21, 1921 drained maxillary sinuses and removed nasal polypi on left side, and attempted to establish intranasal drainage of frontal sinuses "

Patient was discharged from hospital March 28th Chart shows that she had no urticaria or diarrhea since the first nasal operation and the asthma is very much improved

She was re-admitted May 15, 1922 There had been no recurrence or urticaria or diarrhea since leaving hospital, but has been having spells of asthma for three months On May 21st, six days after admission, Dr Hall did an open operation on both frontal sinuses, and found a small quantity of pus and polypi in each She was discharged from the hospital July 2d, much improved in every way She had not had a spell of asthma for four weeks

Her third admission to the hospital was March 7, 1923 Her general health was markedly improved There had been a gain in weight of 28 pounds She had been symptom free until three months ago, when the asthma recurred The blood examination at this time showed Hemoglobin 90 per cent, red cells 4,600,000, leukocytes 11,500, polymorphonuclears 64 per cent, lymphocytes 29 per cent, transitionals 4 per cent, eosinophils 3 per cent

A nose examination by Dr Hall showed a recurrence of the nasal polypi An injection of $\frac{1}{8}$ grain of pilocarpin produced an increase of the eosinophils in two hours from 3 to 7 per cent

With no recurrence of the urticaria or of the diarrhea for over two years following drainage of the nasal sinuses, and partial relief from the asthma, would indicate that all of these symptoms were manifestations of a bacterial anaphylaxis

As there was no evidence of syphilis on the physical examination or in the history, negative blood Wassermann and negative spinal fluid, no arterial disease and no heart disease, the most probable explanation for the hemiplegia was an intracranial complication of the nasal sinus infection and probably a localized pachymeningitis externa. It may be argued that the "drawing of the leg and arm" preceding the coma indicated a Jacksonian epileptic convulsion, which produced a hemorrhage of the brain that caused the hemiplegia. Granting the possibility of this, it still seems fair to assume that the most probable cause for the convulsions was some process in the cortical region due to the sinusitis

Case II—Hemiplegia, with Recovery, in a Case of Frontal Sinus Infection—Dr M, a physician, was first seen at the Eastside Hospital in November, 1916, on account of a right-sided hemiplegia with aphasia that had come on five days before. He began having headaches six or seven years previously, and they had been almost daily and increasing in severity for one year. The pain was always in the left frontal region and radiated to the temporal region and to the left ear. At times the scalp on the left side of the head was so sore that he could hardly comb his hair. The pain would come on at any time, day or night. The day the paralysis came on the headache began at 9 A M, and was unusually intense, requiring several doses of aspirin, acetanilid, and codein for relief. At 4 P M he fell asleep and apparently became comatose, as it was impossible to arouse him. On regaining consciousness at 8 P M he had aphasia and was paralyzed on the right side of his body. He had no convulsions. The aphasia cleared up in five or six days and the hemiplegia in two or three weeks, but the headaches continued for two months, when he had a discharge of $\frac{1}{2}$ ounce of pus from the left side of the nose after using a Sorensen suction-pump. He has

not had a severe headache since. The tenderness over the frontal sinus subsided in a few days. There has been no operation on the sinus. He uses the suction-pump every month or two on account of a feeling of fulness or discomfort, always with complete relief.

There was nothing in his past or personal history of importance except the history of headaches. Three months before an x-ray picture of his head showed a cloudiness of the left frontal sinus. He was thirty-six years old, married, and had 2 living children. There were no children dead and his wife had no miscarriages. He never had syphilis or gonorrhea and did not use alcohol. He had typhoid at sixteen. There was no history of an injury to the head. Except for an occasional head cold there was no history of nose trouble.

I saw him first five days after the onset of his paralysis, and found nothing of importance on examination except a spastic paralysis of the right side, with a slight aphasia and tenderness over the left frontal sinus. The pupils were equal, round, and reacted to light. The temperature was normal, pulse 64, blood-pressure 110 over 70. The urine was negative and nothing abnormal was found on examination of the heart, lungs, or abdomen.

In evaluating the important points in the history and findings the most important ones—namely, tenderness in the left frontal region and x-ray evidence of cloudiness of the left frontal sinus—were ignored. As the patient was improving a probable diagnosis of syphilis was made. The other physicians in attendance concurred in this diagnosis. However, four blood Wassermanns and three spinal fluid tests made in three different laboratories, and negative reactions found in all, left the diagnosis of syphilis without support.

Up to the present time, seven years since the hemiplegia, the patient has been well and his findings now are negative. During this time nothing has developed to indicate any other cause for the intracranial lesion than a sinusitis.

The important features in this case are headache for a number of years, tenderness over the left frontal sinus, cloudiness of

the sinus in the roentgenogram, severe headache for eight hours, coma followed by right-sided spastic paralysis with aphasia, and relief of the headache following drainage of the sinus

Conclusions—The outstanding fact in this case, as well as in the previous one, is that a young adult, without any abnormal condition found except long-standing paranasal sinus infection, develops hemiplegia and recovers. From this the inference seems justified that the cause of the hemiplegia was chronic infection of the accessory sinuses of the nose. There may be some doubt about the nature of the intracranial lesion, but a pachymeningitis seems most probable. This assumption is supported by the fact that the lesion was cortical, obviously circumscribed, was not associated with fever or other signs of a septic condition, and terminated in a complete recovery. Furthermore, from the anatomic relationships existing between the frontal sinus and the dura, a pachymeningitis externa can be readily explained. Infection in the sphenoidal and ethmoidal sinuses are less likely to cause cortical lesions, but undoubtedly are important factors in some of the obscure lesions of the base of the brain and of the cranial nerves. Intracranial complications, with or without recovery of infections of the accessory sinuses of the nose probably occur oftener than is generally recognized, and the importance in considering such infections in all cases of chronic headache and obscure brain lesion cannot be too strongly emphasized.

CLINIC OF DR L S MILNE

BELL MEMORIAL HOSPITAL, UNIVERSITY OF KANSAS

HODGKIN'S DISEASE

HODGKIN'S disease is a condition admittedly only very partially understood and, unfortunately, also veiled in the greatest confusion. There are a variety of synonyms applied to this condition, and its differential diagnosis is often, even usually, difficult or uncertain, and its types and mode of onset very varied.

The following cases are illustrative of some of these types and are of some interest in relation to their diagnosis and therapeutic results.

Case I—An extremely well-developed muscular male, age thirty-three, weight 185 pounds, on May 1, 1922, noticed a painless swelling in the first interspace on the left side immediately against the sternum. This gradually grew till it became quite noticeable, protruding about $\frac{1}{2}$ inch and overlapping the sternum by about $\frac{1}{2}$ inch. Five months later both axillæ developed enlarged glands, and small glands appeared later in the neck, particularly just above the clavicles on both sides. There had been some loss of weight, but this had been regained. Fever has not been complained of, but there had been a progressive loss of strength and energy, and sometimes pains in the chest and some dyspnea on exertion. There was a history of malaria two years ago, typhoid twelve years ago, and several attacks of tonsillitis. He was married, had 2 children, and had an excellent family history.

On first examination, October, 1923, he had a temperature of 100° F, had a mass as above described in the anterior chest,

glands size of walnuts, discrete and hard, not tender, in both axillæ, similar glands size of hazelnuts in the groins, and a chain of glands in the neck on both sides, largest above the clavicles

No masses were felt in abdomen and no enlargement of liver or spleen observed

The other examination, including the urine, was negative except for slight enlargement of the tonsils, which both contained some pus

Blood examination Hb 90, R C 5,089,000, leukocytes 8100, polymorphs 75 per cent, small lymphocytes 15, large lymphocytes 6, large mononuclears 2 per cent, eosinophils 0.5 per cent, basophils 0.5 per cent. No malaria. No nucleated erythrocytes. Wassermann reaction negative

The x-ray of the chest showed extensive enlargement of the mediastinal lymph-glands and also of the hilus bronchial glands. Section of the sternal mass showed a tissue largely composed of lymphocytes embedded in apparently inflammatory tissue, where there was also evidence of proliferation of endothelial-like cells and some few eosinophilic staining types

During the next month the glands increased slightly in size, and weakness became more marked and occasional night-sweats developed. The temperature varied greatly some days, but for the greater part of the time averaged about 100° F

A variety of diagnoses were possible in this case. He had been considered tuberculous, yet the glands showed no evidence of breaking down and were very generalized, and on x-ray examination there was no pulmonary involvement. The tuberculin reaction was also negative, as also was the microscopic examination of the tissue. As against a case of lymphosarcoma he had the same generalized gland involvement to contend with. Also the intermittent character of the progress of the disease and the microscopic examination, although suggestive, was more such as observed in cases of Hodgkin's disease

As an interesting feature of this case he received a number of x-ray treatments covering the areas of glandular involvement, following each of which he had one or two days of fever

and general discomfort At the end of one month no glands could be palpated anywhere All fever had disappeared and his strength had been regained to an extent that he claimed to feel absolutely well

March 10, 1923, six months later, small gland size of pea appeared in the neck above the right clavicle Temperature arose to 99.5° F, and in the next two weeks some glandular enlargement again noticed in both axillæ, and he had some slight hacking cough Again two x-ray treatments were given, with disappearance of the glands, fever, and cough July, 1923 again noticed some small glands in neck, this time treated with radium, with some improvement At the present day his exact condition is that of considerable general weakness, no great loss of weight, and only a few glands palpable in the neck, and a blood-count approximately the same as on first examination

Unfortunately, in this type of disease we can only be speculative, yet it seems to represent a type of Hodgkin's disease The essential picture being general adenopathy, some fever and general debility, and not much loss of weight, with a peculiarly extensive mediastinal involvement with the only other pathologic coexisting condition being chronic tonsillitis and presenting at least in the period under observation no particular alterations in the blood elements It also presented a case greatly improved by x-ray radiation therapy

Case II—A rather slender, small woman, aged fifty-seven, married twelve years, no children She had a history of having a few small lymph-glands in the upper anterior triangle of the neck on both sides since childhood Two years ago hard, discrete, painless masses began to develop throughout the entire anterior triangle on both sides of the neck, becoming of such size as to interfere with the movements of the neck Later, especially in the last year, the axillary glands on both sides had become enlarged to the size of walnuts, several of such size being in both axilla There had been a severe hacking cough during the last six months

In the last three months she had lost weight slightly and had become very weak and easily fatigued

There had been no previous illness except some pain at times in the neck and shoulders during the last seven years

On first examination, July 6, 1913, the masses above described were found in the axillæ and neck and a few smaller glands in the groins. The heart, lungs, and abdomen were negative on examination. Urine negative. Blood Wassermann negative. Von Pirquet negative. Hb 70 per cent, R B C 3,750,000, W B C 30,000, polymorphs 96 per cent, small lymphocytes 3 per cent, large lymphocytes 1 per cent, eosinophils none found, no normoblasts, no poikilocytosis, slight anisocytosis. July 20th, after six x-ray therapeutic exposures, covering all gland-enlarged areas and from which she had no reactions, felt infinitely stronger, better than in years, glands enormously reduced in all areas, W C 10,400. September 18th, after two more x-ray treatments, glands all gone, no fever, felt entirely well. x-Ray of chest also showed almost complete disappearance of the masses which previously had extended outward from the hilus of the lung, and which in all probability had been the essential cause of the severe coughing she had suffered from. On October 10th still feels entirely well, no glands palpable, blood-count normal.

This case differs from the previous one by reason of its more chronic and more extensive involvement, yet, in spite of this, there being a quite different blood-picture and one not particularly frequent in Hodgkin's cases, that of a polymorphonuclear leukocytosis. In the average a lymphocytosis, with, later on, the appearance of large mononuclear types and eosinophils, is more usual. As against an early leukemia, the spleen was not enlarged, there was no predominance or particular number of embryonic cells in the blood, and the glands were especially localized in the neck and bronchial region.

Case III—A tall, rather slender woman, aged twenty-five, married, no children. She had been complaining for four years of tiredness, weakness, and nervousness, and with an occasional

temperature about 99° F, has never coughed or had any expectoration, nor did x-ray examination in March, 1922 reveal any other change than some enlargement of the bronchial hilus glands

Her previous history, as also her family history, was negative Tonsillectomy two years ago Her average weight was about 145 to 150 pounds In April, 1922 she became much weaker, and the temperature ranged to 103° F or more daily This fever continued for almost three months, and although at the end of this period the weight had gone down to 95 pounds, she still maintained a fair amount of strength, which, in addition to the fact she never coughed, appeared quite remarkable for the tuberculous case she was supposed to be In May, 1922, several weeks after this, fever began to reach the higher levels, the lymphatic glands in the neck and axillæ simultaneously began to enlarge, but particularly so above the clavicles These glands were discrete, hard, and of average size of hazelnuts to walnuts in several instances The glands rather rapidly appeared and then slowly increased in size At first there was reported to be a slight lymphocytosis Later examination revealed an average blood-count Hb 80 per cent, R B C 4,600,000, W B C 7600, polys 54 per cent, small lymphs 33 per cent large lymphs 6 per cent, large mononuclears 4 per cent, eosinophils 2 per cent, basophils 1 per cent x-Ray of lungs negative, but bronchial glands larger

In July, 1922 x-ray therapy started In three weeks after first exposure all fever had ceased, and the palpable glands were reduced in size and number until only three small masses appeared above the left clavicle Later several more x-ray treatments were given, and by November, 1922 she felt very well and weighed 145 pounds

December 30, 1922 no menstruation for two months, pregnant February 19, 1923 Aborted May 7th No treatment since November, 1922 Again fever to 100° F, feels very weak, glands again palpable, though small on both sides of neck above clavicle x-Ray therapy again tried, with no particular results The glands remained enlarged and she did not improve physically

as in the first course of treatment, and to date had continued losing weight, but not equally in strength, and her glands still are, although small, palpable in the neck

This case illustrates a type beginning with constitutional symptoms, later glandular involvement, severe and prolonged pyrexia and loss of weight, no marked blood changes, at least in the period under investigation, and a surprising initial x-ray therapeutic result

Case IV—A contrast to the 3 preceding cases, and one which from certain viewpoints could be classified under the caption of Hodgkin's disease, but which also, and more probably, is related to another disease group

The patient was a well-developed, robust man, aged twenty-three, a hotel waiter, who had come under observation for the early secondary stage of syphilis eighteen months before his death. The inguinal nodes at this time were slightly swollen, but the spleen and liver were not apparently enlarged. The urine showed no special change. His blood was not examined at this time. He had suffered from gonorrhea five months previous to his coming to the hospital, but denied any other illness before this. There was no history of any previous enlargement of the lymph-nodes. He had originally come from Greece, but had been in the United States for seven years. His parents were both alive and healthy. He had one brother who also gave a history of having acquired syphilis recently, and who presented some enlargement of the cervical and axillary glands, and the spleen and liver were both slightly larger than normal. He had not, however, noticed these himself. The blood also showed practically the same picture as did the patient's in the early stages. He returned shortly afterward to Greece, so that the further course of his disease could not be traced. The patient remained in the hospital for five weeks, and was treated with intramuscular mercury injections. These were continued at his home for six months, and for the next four months he took internal mercury treatment.

Examination — A few weeks after this time, about six months

before his death the patient re-entered the hospital complaining of a recent swelling of the lymphatic glands of his neck. The axillary and inguinal nodes were also found to be slightly enlarged. The spleen extended 3 inches below the costal margin. The liver also was slightly enlarged, its lower border being palpable 3 inches below the costal margin in the right mid-clavicular line. His blood-serum gave a positive Wassermann reaction and the blood-count at this time showed marked anemia.

Red blood-corpuscles	3,400,000 per cmm
Hemoglobin	55.0 per cent
Leukocytes Differential count	52,000 per cmm
Polymorphonuclear leukocytes	10.5 per cent
Transitional—polymorphonuclears to myelocytes	3.4 "
Myelocytes (finely acidophil granular)	5.6 "
Eosinophil polymorphonuclears (coarse granular)	1 "
Eosinophil myelocytes (coarse granular)	1.3 "
Small lymphocytes	11.2 "
Medium sized lymphocytes	30.7 "
Large lymphocytes	19.3 "
Large mononuclears, clear cytoplasm, vesicular nucleus	8 "
Medium sized mononuclears, finely basophil granular	1 "
Large sized mononuclears, finely basophil granular	2.9 "
Mast cells	0.7 "
Normoblasts (compared with leukocytes)	4.1 "
Megaloblasts (compared with leukocytes)	0.3 "

The patient's weakness increased rapidly. The cervical nodes, as well as those in all the lymphoid situations throughout the body, became rapidly larger, and breathing through the nose became progressively more difficult. He developed effusions, which had frequently to be removed, from his left pleural cavity, and occasionally also from the right. The spleen increased considerably in size and the anemia became much more pronounced. The leukocytes in the blood varied from 30,000 to 73,000, a rather large number being present just before death. The relative proportions remained about the same. The eosinophils, however, both polymorphonuclears and eosinophils, and the neutrophil myelocytes became slightly increased, the neutrophil polymorphonuclears slightly reduced while the large finely

basophil granular mononuclears rose finally to 89 per cent. The number of normoblasts remained proportionately about the same, but the megaloblasts had increased to 27 per cent on the day of the patient's death. The red blood-corpuscles had become progressively reduced, as also had the hemoglobin, the color-index, however, being always under 1. No malarial parasites were found in the blood at any time. The temperature had a slight daily variation, as an average rising in the evening to between 99.5° to 100° F, but sometimes reaching 100.8° F, as a maximum and 97.6° F as a minimum. Various medications, including arsenic, mercury, and iron, were used, with no apparent improvement. The patient died in an extremely asthenic but well-nourished condition.

Necropsy—A few hours after death the lymph-nodes all over the body were found greatly enlarged, firm, elastic, more or less discrete, and of a pink color, although some were dark purple from hemorrhage. In the axillæ and groins some of these had attained the size of a hen's egg. Microscopically, the nodes were shown to be enlarged, not only by infiltration of cells from the blood but also by an active proliferation locally.

An opening into the thorax revealed several large lymph-nodes in the anterior inner part of the right vault of the diaphragm. One large hemorrhagic node was situated at the inner anterior part of the left vault, close to the attachment of the pericardium. The outline of the pericardium was regular and its outer surface smooth, on section, it was found to be enormously thickened. Posteriorly it measured 5 mm in the middle and 1 cm in the upper part. The lower portions in the region of the apex were only moderately thickened. Anteriorly, however, between the levels corresponding to the fourth rib and the upper border of the manubrium sterni, there was a special thickening about 4 cm in diameter. This was in direct continuity with the pericardium and extended below the level of the fourth rib, gradually becoming thinner toward the apex, where it was only about 3 mm in thickness. This extensive pericardial thickening was firm, apparently fibrous, and of a pale yellowish-pink color. In its upper part it included several small lymph-nodes, into

some of which there were hemorrhagic extravasations. The bronchial nodes were considerably larger, some of them also being dark red from hemorrhage. Microscopically this condition in the upper part of the pericardium was found to be composed for the most part of fairly dense fibrous tissue, which included very frequent, rather ill-defined, lymphoid foci which resembled closely the structure of the hyperplastic infiltrated lymph-nodes in other situations. This mass did not correspond to a tumor in growth, but seemed to be the result of hyperplasia of the anterior mediastinal nodes and most probably also of the thymus. No Hassall's corpuscles, however, were found. In addition to this lymphoid hyperplasia the thickening around the pericardium was associated with an extensive chronic inflammatory matting, and leukemic infiltration, also, to some extent had assisted in the process. The inner surface of the pericardium was smooth and there was no excess of fluid in the pericardial sac. There were no evidences of tuberculosis in the nodes throughout the body or in the pericardial thickening. Nor were there any signs which made syphilis in any way a certain factor, no spirochetes were found in any of the tissues examined in various situations throughout the body. The left pleural cavity contained a large amount of blood-stained fluid. The pleura showed a chronic thickening due, as seen microscopically, to leukemic infiltration and chronic inflammation. The heart was dilated and flabby.

The spleen weighed 900 gm and was 21 cm long by 14 cm wide. It was of a dark reddish color and moderately firm. The malpighian bodies were markedly enlarged appearing as white spots through the section. Microscopically the perivascular spaces were considerably distended by accumulation of cells. The sinuses also were frequently almost filled for the most part with small mononucleated cells. All the types seen in the blood were to be observed in these sinuses. There seemed, however, to be a very considerable proliferation of the lining endothelium. In some of the cells of this proliferation there were apparent distinct evidences of new formation of nucleated red blood-cells. Some of the endothelial cells also seemed to be

the seat of a deposit of coarse eosinophil granules, at first, apparently deposited around or on one side of the nucleus. Some of them could be observed in process of direct division, and some also could be observed in the perivascular tissues. They never, however, assumed quite the appearance of the eosinophil myelocytes as observed in the peripheral blood.

The liver was moderately enlarged, weighing 2150 gm, and microscopically showed a moderate deposit of hemosiderin pigment in the liver cells, and a considerable infiltration in the portal spaces, consisting mostly of lymphocyte-like cells, although the other types seen in the blood were also represented. Many of these cells were situated perivascularly, but the capillaries themselves frequently were crowded with nucleated cells. To some extent in the perivascular spaces, but more in the interior of the vessel, there could be observed a relatively large number of coarsely granular eosinophil cells, mostly small, frequently appearing attached to the vessel wall, and containing small, round, homogeneous, darkly stained nuclei, which were similar to those observed in the spleen. The lining endothelium of the capillaries, in isolated places in the interior of the lobules, also showed considerable proliferation, some of this apparently assisting in the production of leukocyte types, such as were seen in the blood. To a small extent also the formation of nucleated red blood-corpuscles could be determined.

The kidneys were extremely enlarged, the left weighing 700 gm, the right, 750 gm. They were, for the most part, pale, yellowish pink, and contained numerous small hemorrhages, chiefly in the cortex. Microscopically the enlargement was due not only to the hemorrhages but also to a very extensive leukemic infiltration. In the perivascular spaces, besides a large number of small, mononucleated cells, small clumps of relatively large cells could frequently be observed, having some of the appearances of myelocytes, and generally containing numerous fine acidophil granules. Some of these myelocyte-like cells, although not quite resembling any type found in the peripheral blood, could also be seen isolated in the kidney capillaries. The intestines showed no specially abundant aggregations of lymphoid tissue.

The bone-marrow was unusual for a case of leukemia, being dark red in color, in several situations examined it was almost wholly erythroblastic. There was a relatively small infiltration of leukocytes from the blood, but only a very slight formation of polymorphonuclears, myelocytes, and eosinophils. The reason for this almost exclusively erythroblastic marrow may have been that the destruction and loss of red blood-cells was specially severe, and that the usual site of new erythrocyte formation, the bone-marrow, had become practically entirely devoted to its production, assisted to a considerable extent, as has been mentioned, by the spleen and liver. A great proportion of the leukocytes found in the blood was evidently derived from some other source than the bone-marrow. The greater part of the lymphocyte-like cells, for instance, were evidently derived from proliferation processes in the lymph-nodes, and from endothelial surfaces in other tissues. In connection with the consideration of the development of the neutrophil and eosinophil myelocytes in the blood, it may be again noted that numerous coarsely granular eosinophil cells were found in apparently all stages of formation in the spleen, to a less extent in the liver, and occasionally in the lymph-nodes.

Clumps of large, very finely acidophil granular mononuclear cells were also found in the kidneys. These clumps, of course, may have been formed by local proliferation from some of the cells which had penetrated from the blood and locally developed but they also presented evidences that some of them had entered the blood subsequently. These may have been responsible for the production of some of the myelocytes observed in the peripheral blood. Occasionally also in the peripheral blood myelocytes of both types were found in process of division.

This case presented a most unusual blood-picture, yet one that is not uncommonly observed in case of Hodgkin's disease. There was, however, a most extensive involvement of many internal organs, at least their capillaries were enormously distended with embryonic cells such as is observed in cases of leukemia. The whole picture is one of an unusual atypical type of leukemia, yet the differential line between leukemia and Hodg-

kin's disease may be, in some instances, as in this case, a rather fine distinction

Hodgkin's disease, as illustrated by these 4 cases, is very varied in its clinical forms. In about 90 per cent of cases its occurrence is at about thirty years of age and about three times commoner in males than females. As concurrent, or possibly etiologic factors, there seems to be some throat, nasal sinus, or dental infection foci, although gastro-intestinal, genito-urinary, or skin infections are also found. In this relation, particularly in throat infections, as described by Naegali, Cabot, Turk, Morse, Cross, Downey, McKinley, etc., cases do occur of acute cervical or general adenopathy and some lymphocytosis in the blood which at first resembles the onset of either a leukemia or Hodgkin's disease, yet which seems to get wholly well in a short period of time. In Hodgkin's cases at least 60 per cent of the glands enlarge first in the neck and the involvement may remain there in some instances. The whole course of the disease seems to be dependent on the entrance into the system through the lymphatics of some infection the nature of which is not clearly known. There may even be a variety of organisms producing the different clinical types of this disease. In 1910 Frankel and Much found in the residue of excised glands certain anti-formin-resisting organisms which they regarded as a non-acid-fast form of the tubercle bacillus. Later Negri, Bunting and Yates, Rosenow, and others isolated from the glands a pleomorphic diphthyroid, an organism which has been under much discussion, but which seems to be generally conceded to be a saprophyte found in many types of diseased tissues. Hodgkin's disease can be definitely said, from its pathology and clinical course, to be not of tuberculous origin, nor does it conform to all of the essentials of a tumor, although sometimes at certain stages rather confusing.

It is, however, a distinct clinical entity at first causing often for months even years, certain constitutional symptoms, such as asthenia, fever, which may be considerable and over a long period of time (Case III), loss of weight, etc. This phase may be absent and the glandular enlargement be first evident. It

first there occurs a hyperplasia of the lymphoid cells, soon destroying the architecture of the gland and associated with a greater or less degree of lymphocytosis in the blood. Later the fibroid stroma of the gland and the endothelial cells proliferate and the glands assume a more fibrous appearance, and with this certain endothelial elements and eosinophils appear in the blood. Some few cases, as noted in Case II, appear to show essentially a polymorphonuclear leukocytosis, which again argues that the nature of the infection may not be the same in all cases.

With this glandular change and endothelial hyperplasia there is a destruction of erythrocytes and anemia of greater or less degree supervenes.

The glandular enlargement, although most prevalently in the neck, may be general or may particularly involve the bronchial glands, causing the most marked symptoms to be cough or asthma, a condition, which if co-related to the fever, as it often is, makes a diagnosis of tuberculosis difficult, the blood changes at the beginning being similar, and often it is only cleared up by x-ray examination. In some cases the glands may be mainly enlarged in the mediastinum with essentially cardiac symptoms. Even more difficult are those cases which involve the abdominal glands primarily causing diffuse gastro-intestinal symptoms and often causing obstruction of the thoracic duct and a chylous ascites. In some of these abdominal cases there may be great involvement of the spleen with considerable splenomegaly, a condition leading to difficulty in differential diagnosis from splenic anemia, some of which cases, as described, also may have been cases of Hodgkin's disease.

Where there is considerable leukocytosis, some glandular enlargement, and some spleen involvement, the differential diagnosis from leukemia is difficult, if not impossible. In leukemia, however, the embryonic elements are more prevalent in the blood. The leukocytosis tends to higher figures and the disease is more generalized. In Case IV the blood is suggestive of one of the stages of Hodgkin's disease, although the autopsy is that of leukemia. Indeed, leukemia probably also is a reaction to some focal infection not unlike that responsible for Hodgkin's

disease Not fully understanding the etiology of Hodgkin's disease, the treatment is naturally uncertain Surgery is of practically no avail and medical measures are equally unsatisfactory Vaccines, with any organism, seem also worthless

The only treatment which has proved of some value is x-ray radiation therapy, and, as noted in these 3 cases, was extremely beneficial, although probably not lasting in its effect This success with x-ray radiation is usually most noticeable in the early cases, especially those in which the glands have not yet become fibrous

It seems also certain that should there be discovered some septic focus—tonsils, teeth, sinuses, etc—in the line of lymphatic drainage from the initially enlarged glands, that such focus be removed

Finally, it seems reasonable to suppose that in this era of research that the exact etiology of this not altogether and usually misunderstood disorder will be exposed and some rational radical curative therapy will be instituted

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THE USE OF VOLUME INDEX IN THE STUDY OF THE BLOOD IN ANEMIA

I WISH to emphasize the importance of knowing the relative mass of the red blood-cells in the differential diagnosis and prognosis of anemia. A careful study of the blood of a patient suffering from anemia necessitates the use of all methods of examination which may yield information of value. In determining the type one wishes always to know the number and character of the white cells, the level of the platelets, and the morphologic changes in the red cells, as well as the hemoglobin content and the red cell count. In certain cases it is important to determine the coagulation time, the fragility of the erythrocytes, and the percentage of red cells taking the vital stain.

Probably the criterion on which most reliance is placed in differentiating types of anemia is, however, the relationship between the number of red cells and the hemoglobin, which is expressed as the color index. Anemias which are secondary to increased blood loss or an impairment of bone-marrow function are associated with a color index less than 1.00 while the primary anemias with the exception of chlorosis usually have a color index greater than 1.00.

The color index is calculated by dividing the hemoglobin in percentage of normal by the red cells in percentage of normal. It is often assumed that the color index represents the percentage of hemoglobin in the red cells. Little consideration is given to the fact that the size of the average red cell varies greatly under different conditions. The color index indicates only the amount of hemoglobin per cell relative to normal. It is de-

pendent upon both the volume of the red cells and the percentage of hemoglobin in the red cells

Capps¹ in 1903 introduced the term "volume index" to indicate the volume of the average red cell relative to normal. It is calculated by dividing the volume of packed red cells in percentage of normal by the number of red cells in percentage of normal. To determine the relative mass of the red cells Capps utilized the hematocrit of Daland. This instrument consists of a capillary tube which is filled with blood and whirled in the centrifuge. Only the mass of the red cells relative to normal can be determined, absolute values are not obtained. Capps pointed out the fundamental facts to be derived from a study of the volume of the red cells. He noted that the color index is never greater than the volume index, that the volume index is usually greater than 1.00 in pernicious anemia, and usually less than 1.00 in secondary anemia. He found, however, a volume index greater than 1.00 in certain conditions other than primary anemia, such as jaundice. He compared the volume index with the color index calculated with hemoglobin determinations made by a relative method, namely, that of von Fleischl.

In determining the mass of red cells I have utilized a method which requires no special apparatus, gives absolute readings which are exceedingly constant and accurate, and affords data from which certain calculations other than the volume index may be made. The method was suggested by Hooper, Smith, Belt, and Whipple² for use in determining blood-volume. Ten c.c. of blood are run into an accurately graduated 15-c.c. centrifuge tube containing 2 c.c. of 1.6 per cent sodium oxalate, an isotonic anticoagulant. The tube is then whirled in a centrifuge for one-half hour at high speed. Maximum packing for the centrifuge used should be attained during this period. A red cell count is made simultaneously, preferably on oxalated blood. The number of cubic centimeters of packed cells which is obtained from 10 c.c. of normal blood with a count of 5,000,000 must be known for the centrifuge used. We have found this to be 1.8 c.c. or 48 per cent, with an International centrifuge size 1, type A, with a 12-inch head. With a very much more

powerful centrifuge used earlier in our work the average was found to be 46 per cent. The volume percentage of cells in terms

DIAGRAM TO ILLUSTRATE THE VOLUME OF PACKED RED CORPUSCLES OBTAINED ON CENTRIFUGING 10 cc OF BLOOD CONTAINING 5 MILLION RED CELLS PER CUBIC MILLIMETER

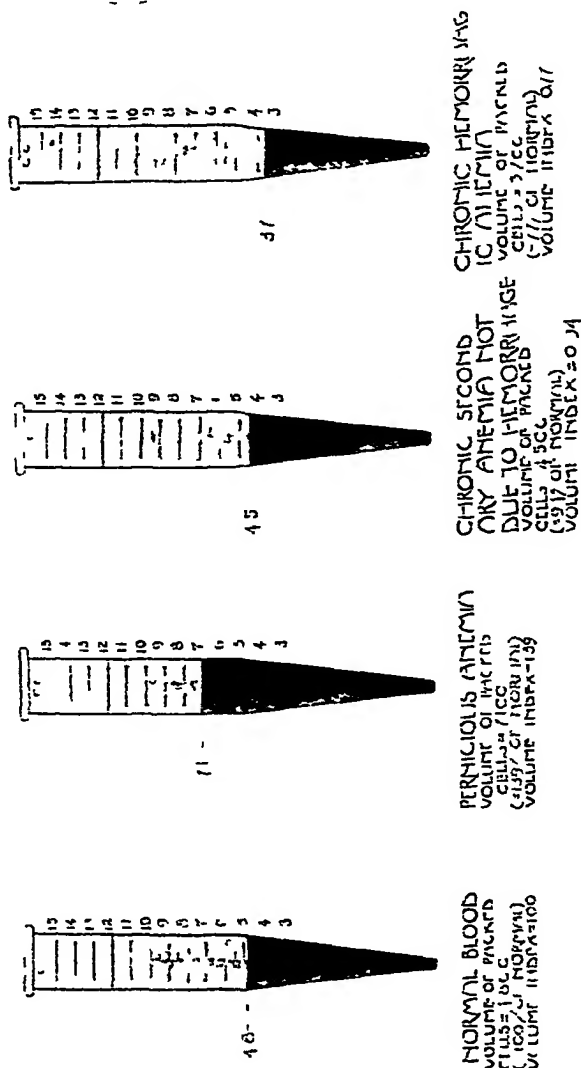


Fig 179.

of normal for any blood is the actual number of cubic centimeters of packed cells obtained from 10 cc of blood divided by 4.8

(Fig 179) The volume percentage of red cells is analogous to the hemoglobin percentage. When determined in this manner the volume index is very constant.

The color index is subject to many inaccuracies. A correct determination requires first of all a careful hemoglobin reading. There is probably no laboratory test which gives more widely varying readings in different hands than a hemoglobin determination. This variation is due to the frequent use of instruments which are technically inaccurate, and to the fact that few instruments read as 100 per cent the hemoglobin of a normal blood with a red cell count of 5,000,000. With the same blood one instrument may read 70 per cent, while another will read 120 per cent. It is evident that a color index calculation on such a basis is of little value. The color index of normal blood should be 1.00. Emerson states, however,³ that taking instruments as they come, the color index in normal individuals varies from 0.80 to 1.00.

The only direct method of hemoglobin determination which is available for clinical use is the ferricyanid method of Haldane as adapted by Van Slyke⁴ to his blood-gas apparatus. This method should be the one of choice where accurate estimations are necessary, or of value. I have made hemoglobin determinations on 52 normal individuals with the Van Slyke apparatus, and have found that the average number of grams of hemoglobin per 100 c.c. of blood per 5,000,000 cells is 15.6.⁵ This figure I have taken as 100 per cent in calculating all hemoglobin percentages.

The necessity for accurate red cell counts in calculating color and volume index should also be emphasized. Many of the pipets and counting chambers on the market are inaccurately calibrated. For the most careful work it is best to make the red cell counts on oxalated blood withdrawn by venipuncture.

The actual concentration of hemoglobin in the red cells may be determined by dividing the hemoglobin in grams per 100 c.c. by the number of cubic centimeters of packed cells obtained per 100 c.c. of blood. The same result is obtained by dividing the hemoglobin in per cent by the volume percentage of cells.

or the color index by the volume index. This index which expresses the amount of hemoglobin per unit volume of cells I have called the "saturation index".⁷⁷ The values for the color, volume, and saturation index in normal individuals and in different types of anemia are discussed below. The color index in every case is based on hemoglobin determinations by the ferri-cyanid method in the Van Slyke apparatus.

NORMAL BLOOD

The normal individuals studied included 20 men between the ages of eighteen and thirty, 20 between thirty and fifty, and 12

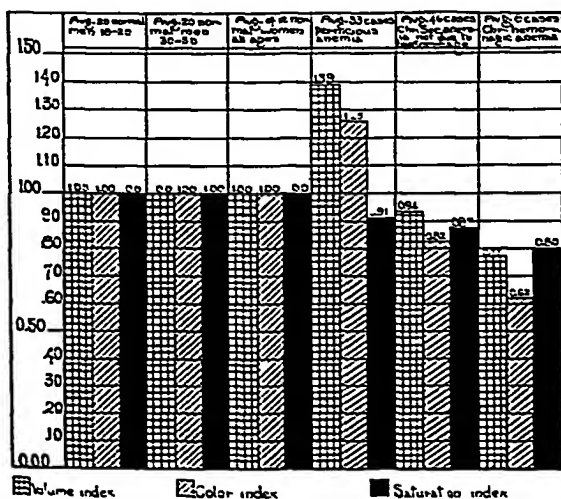


Diagram to show the volume color and saturation index in normal blood and in the anemias

Fig 180

women from eighteen to fifty years of age. The average color, volume, and saturation index for the total number and for each of the three groups is 1.00 (Fig 180). We have considered all determinations from 0.95 to 1.05 as within the limit of technical errors. Few of the 52 determinations were outside these limits. The actual findings in 10 typical cases are shown in Table 1. The results obtained indicate that the volume of the average

normal red cell is practically constant. I am inclined to think that even such slight variations as were obtained are due to errors in technic rather than to an actual difference in cell volume. Likewise the amount of hemoglobin in the cells per unit volume as indicated by the saturation index is very constant. It follows that the color index is also 1.00 within the limits of error of the calculation. The actual percentage of hemoglobin in the cells is 33.9 per cent (Table 5). This figure evidently represents the maximum saturation of the cells with hemoglobin, since it is never higher. The great constancy of the volume of the average red cell and the amount of hemoglobin per unit volume serves as an excellent base line with which deviations in the anemias may be compared.

TABLE 1

TYPICAL COLOR, VOLUME, AND SATURATION INDICES IN NORMAL INDIVIDUALS

R. B. C. in M. per c.mm.	Hemoglobin in per cent	Volume percent of R. B. C.	Color index	Volume index	Saturation index
5.26	105	106	1.00	1.01	0.99
5.57	110	111	0.99	1.00	0.99
4.80	96	100	1.00	1.04	0.96
4.32	89	87	1.03	1.00	1.03
5.16	103	103	1.00	1.00	1.00
5.05	99	100	0.98	0.99	1.01
4.26	86	85	1.01	1.00	1.01
5.49	107	107	0.97	0.97	1.00
4.52	90	96	0.95	0.99	1.01
4.64	92	92	1.00	1.00	1.00

SECONDARY ANEMIA

A secondary anemia is dependent upon increased blood loss, a depression of bone-marrow function, or a combination of these two factors. The most striking finding in the chronic secondary anemias due to hemorrhage is the very small cell volume. The average volume index in 8 cases is 0.77. The color index is still lower—0.62. The saturation index is 0.80. In the group of secondary anemias not due to blood loss by hemorrhage the volume index is never higher, and in many cases it is below normal. The color index here also is never greater and often less than the volume index. The average volume in 38 cases of this type of anemia is 0.94, the color index 0.82, and the saturation index

0.87 The actual concentration of hemoglobin in the cells is 30 per cent. In studying 82 cases of anemia to date by the method outlined, no secondary anemia has been found with a volume index greater than 1.00. Typical findings in cases of secondary anemia are shown in Table 2.

TABLE 2

TYPICAL COLOR, VOLUME, AND SATURATION INDEXES IN SECONDARY ANEMIA

R. B. C. in M per c.mm.	Hemoglobin in per cent	Volume percentage of R. B. C.	Color index.	Volume index.	Saturation index.	Diagnosis.
1.96	35	39	0.90	1.00	0.90	Carcinoma of stomach.
2.67	44	52	0.82	0.98	0.85	Chronic bronchitis
3.21	52	65	0.81	1.01	0.80	Lead-poisoning
3.35	59	68	0.88	1.03	0.87	Acute endocarditis
3.36	43	52	0.64	0.78	0.64	Chronic nephritis
2.79	43	44	0.80	0.80	1.00	Oral sepsis
3.42	55	65	0.81	0.96	0.85	Chronic cholecystitis
2.24	39	56	0.88	1.02	0.86	Carcinoma of colon
3.43	34	46	0.50	0.67	0.75	Hemorrhoids
3.93	57	67	0.73	0.75	0.85	Gastric ulcer

One value of the volume index is in differentiating certain cases of secondary anemia from pernicious anemia. The greatest value, however, is in prognosis. The percentage of hemoglobin cannot rise above the percentage volume of red cells. The extent of diminution in size is a valuable criterion of the state of the bone-marrow. Very small cells probably mean an exhaustion of the bone-marrow. The use of volume index in the prognosis of secondary anemia can be best illustrated by an example. A patient with a red cell count of 4,000,000 has a hemoglobin of 40 per cent. The color index is 0.50. Such a color index may be due to the fact that the cells are of normal volume, but only one-half saturated with hemoglobin. The volume index then would be 1.00, and the saturation index 0.50. To recover from such an anemia the cells would have only to be filled with hemoglobin. On the other hand, the color index of 0.50 may be due to the fact that the volume of the average cell is one-half of normal while it is completely filled with hemoglobin. Here the volume index could be 0.50 and the saturation index 1.00.

It is apparent that to recover from this anemia the cells must first of all obtain normal size, which will probably be a slow process. The hemoglobin cannot rise faster than the volume of the cells. Its increase is limited by the increase in volume, and it is easier for the bone-marrow to correct a quantitative deficiency than a qualitative one.

PERNICIOUS ANEMIA

Perhaps the greatest value to be derived from the study of the relative cell mass is found in the diagnosis of pernicious anemia. It has been noted that the volume of the average red cell in normal individuals is remarkably constant and that in secondary anemia the average cell volume is never greater and usually less than normal. The findings in pernicious anemia are in marked contrast to these results. The average volume index in 33 cases of pernicious anemia is 1.39. The average color index is 1.25 (Fig. 180). The saturation index is 0.91, and the actual concentration of hemoglobin in the cells is 30 per cent. The color index is usually above 1.00, but not constantly so. The volume index is always above 1.00, well beyond the limits of error in the determinations, and is always as great or greater than the color index. Typical findings in actual determinations are shown in Table 3.

TABLE 3

TYPICAL COLOR, VOLUME, AND SATURATION INDICES* COMPARED WITH THE QUALITATIVE CHANGES OF THE RED CELLS IN PERNICIOUS ANEMIA

R B C. in M per cmm	Hemo- globin in per cent	Volume percent age of R B C.	Color index	Volume index	Saturation index	Anisocytosis	Poikilocytosis	Nucleated per 500 W B C.
0.84	26	27	1.55	1.61	0.97	++++	++++	25
1.10	26	31	1.11	1.32	0.84	++++	++++	10
1.24	19	33	0.80	1.30	0.62	+++	+++	0
1.52	49	49	1.61	1.61	1.00	+++	+++	25
1.75	35	16	1.10	1.35	0.79	+++	+	0
2.18	57	57	1.31	1.31	1.00	0	0	0
2.27	42	81	0.93	0.77	0.53	+++	+	0
2.41	74	76	1.54	1.57	0.95	+	+	0
2.79	65	69	1.16	1.23	0.94	0	0	0
3.33	80	81	1.20	1.20	1.00	0	0	0

The great value of the presence of large cells in the diagnosis of pernicious anemia has long been recognized. The usual method of estimating the size of the cell is to measure the cell with a micrometer scale. Only one dimension, the diameter, is taken into consideration in the use of such a method of measurement. There may be a very great increase in the volume of cells due to the fact that the cells may approach a spheroid form without a lateral increase in the diameter. In determining the volume of the cells by the hematocrit all dimensions are taken into account.

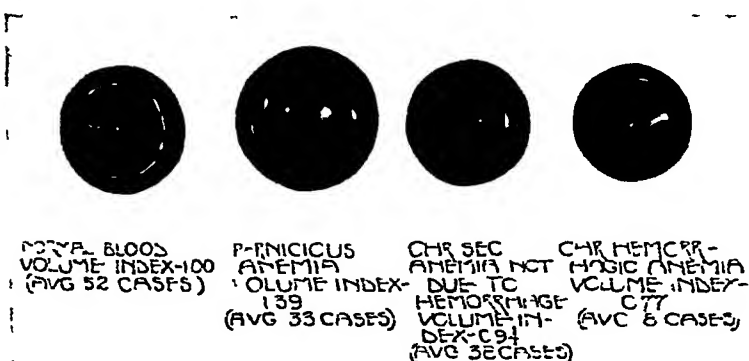


Fig 181—Photograph to illustrate the size of the average red blood-cell in different types of anemia as compared with the normal. Note the relatively small change in diameter corresponding to large differences in volume as indicated by the volume index.

In Table 3 I have also recorded the relative qualitative changes as noted in the stained smear. Marked qualitative changes are seldom apparent until the red count is quite low. In early cases and in remissions where qualitative changes are not apparent, or at least not marked, the volume index is still high. Here the increase in volume is so uniform it is not recognized in the stained preparation. If an increase in cell volume involves all the cells uniformly, as is commonly found in early cases, or in remissions, a very marked increase in the volume will result from only a slight increase in diameter and thickness. The average cell volume may be increased 30 per cent (volume

index 1.39) with an increase of less than a micron in diameter provided the increase affects all cells uniformly. It would be most difficult to recognize such a slight increase in diameter from a study of a stained smear. A photograph of models made to scale corresponding to different volume indexes is shown in Fig. 181.

TABLE 4

THE COLOR, VOLUME, AND SATURATION INDICES OF SECONDARY AND PERNICIOUS ANEMIA AS CONTRASTED WITH NORMAL BLOOD

R. B. C. in M. per c.mm.	Hemo- globin in per cent	Volume of R. B. C. percentage	Color Index	Volume Index	Saturation Index	
5.08	101	101	1.00	1.00	1.00	Average 20 normal men ages eighteen to thirty
4.865	99	98	1.00	1.00	1.00	Average 20 normal men ages thirty to fifty
1.26	85	85	1.00	1.00	1.00	Average 12 normal women all ages
4.74	95	95	1.00	1.00	1.00	Average 52 normal men and women
1.71	41	50	1.25	1.39	0.91	Average 33 cases of pernicious anemia
3.59	58	66	0.82	0.94	0.87	Average 38 cases of secondary anemia not due to hemorrhage
3.57	44	55	0.62	0.77	0.80	Average 8 cases of secondary anemia due to hemorrhage

In studying the blood of 82 persons with anemia, only 3 other than cases of pernicious anemia have shown a volume index greater than 1.00. One patient had aplastic anemia, another congenital hemolytic jaundice, and the third acquired hemolytic jaundice. These 3 patients all showed free hydrochloric acid in the gastric contents. The pernicious anemias had constantly an absence of free acid.

TABLE 5

COMPARISON OF THE VOLUME, HEMOGLOBIN CONTENT, AND HEMOGLOBIN PERCENTAGE OF THE AVERAGE RED CELL IN NORMAL BLOOD AND IN ANEMIA

Volume of the average cell in c.c. $\times 10^{-11}$	Grams of Hb in the average cell $\times 10^{-11}$	Actual percentage of the hemoglobin in the cell.	
9 2	3 11	33 8	Average 20 normal women ages eighteen to thirty
9 2	3 13	34 1	Average 20 normal women ages thirty to fifty
9 2	3 13	34 1	Average 12 normal women all ages
9 2	3 12	33 9	Average 52 normal women and men
13 0	3 90	30 0	Average 33 pernicious anemias
8 6	2 56	30 0	Average 38 chronic secondary anemias not due to hemorrhage
7 1	1 94	27 3	Average 7 chronic hemorrhagic anemias

It has seemed to me that a volume index greater than 1 00 beyond the limits of error of the determination is constant and essential for the diagnosis of pernicious anemia. A plus volume index associated with an achlorhydria is practically pathognomonic evidence of pernicious anemia. A color index greater than 1 00 when correctly determined has the same significance as a high volume index, but is not a constant finding. The fact that the volume index is always as great or greater than the color index shows that supersaturation of the red cells with hemoglobin does not occur. The characteristic high color index is dependent upon an increase in the volume of the red cells. In fact, only a few of the cases of pernicious anemia have a saturation index as great as 1 00, showing that the cells are seldom ever fully saturated. It is interesting to note that the saturation index in all types of anemia even with the wide difference in volume is much the same.

SUMMARY

The color index is subject to numerous errors, due principally to inaccuracies in hemoglobin determinations.

The volume index can be quickly and accurately determined. The volume index or normal blood is practically constant and runs parallel with an accurately determined color index.

Normal blood is completely saturated with hemoglobin.

In anemia secondary to increased blood destruction or inhibition of bone-marrow function the volume index is 1.00 or less.

A low volume index probably indicates a marked depression of bone-marrow function.

In pernicious anemia the volume index is always greater than 1.00, and is always as great and usually greater than the color index.

A volume index greater than 1.00 seldom occurs except in pernicious anemia and is the one constant blood finding in pernicious anemia.

A volume index greater than 1.00 beyond the limits of technical error when associated with an achylia is practically essential, constant, and pathognomonic evidence of pernicious anemia.

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CASES ILLUSTRATING CERTAIN PROBLEMS IN FOCAL INFECTION

DURING the past ten years much has been written concerning focal infection. The rôle of chronic foci of infection in the causation of systemic disease has been overemphasized by many and undervalued by others. Few clinicians at the present time, however, deny that areas of infection in themselves symptomless may give rise to serious metastatic disease.

Certainly the most important contribution so far made to the subject of focal infection is the demonstration by Rosenow that the organisms concerned in chronic foci of infection have a specific tendency to localize in certain tissues of the body. This elective affinity is dependent upon some peculiar inherent property of the infecting organism. Rosenow has shown thus that bacteria recovered from foci of infection tend to reproduce in animals the particular lesion from which the patient suffers. This reproduction of the patient's lesion in animals certainly constitutes the best proof we have of the etiologic relationship of the focus to the disease.

I have used this method of proof in the cases which are presented below as illustrating certain problems encountered in the management of chronic focal infection.

CASE I ACUTE PYELONEPHRITIS FROM A TOOTH SHOWING NO RADIOGRAPHIC EVIDENCE OF INFECTION

Case History—W. M., medical student, age thirty-four, complained of frequent urination, hematuria, chills, and fever. The symptoms had begun two weeks before admission. He had been relieved at the onset by hyoscyamus, but the chills and fever recurred. The patient stated that he had had two other similar attacks.

The general examination was negative. The tonsils had been removed. There was a single pulpless tooth containing a large inlay (Fig 182). A radiograph showed some decay under

the inlay, but no bone absorption or other evidence of infection at the root tip. The examination of the urine revealed gross blood, many pus-cells, and short chain streptococci which produced no hemolysis on blood-agar.

The pulpless tooth was extracted. A culture of the tip in a deep tube of glucose-brain-broth-agar showed many colonies of a non-hemolytic streptococcus. Two rabbits were injected intravenously with 5 c c of a broth culture of the streptococcus. One animal was killed three days after the injection. There



Fig 182—Radiograph of tooth the culture from which showed a profuse growth of a non-hemolytic streptococcus. The injection of this organism into a rabbit produced the kidney lesion shown in Fig 183.



Fig 183—Kidney of rabbit with multiple abscesses in the medulla produced by the intravenous injection of streptococcus recovered from tip of tooth shown in Fig 182.

were numerous abscesses in the medulla of the kidney (Fig 183) and cloudy fluid in the joints. The other rabbit when killed six days after the injection showed a marked acute hemorrhagic nephritis and a few vegetations on the heart valves.

The patient's symptoms cleared up rapidly and the urine returned to normal. There has been no recurrence of the infection to date. The results of the animal inoculations and the relief of symptoms following the extraction of the tooth strongly suggest that the patient's kidney lesion was due to the tooth infection.

Discussion—This case illustrates well a point which is often

overlooked in the consideration of infected teeth as a factor in some systemic disorder. The radiograph is commonly depended upon entirely to determine whether certain teeth are possible foci of infection. A recent study in which over one thousand root tips have been cultured by a quantitative technic revealed the fact that 40 per cent of the pulpless teeth which are negative in the radiograph harbor a sufficient number of bacteria to be a possible factor in systemic disease. No one can translate radiographic findings into terms of numbers of bacteria. Myriads of bacteria may be present about a root tip long before there is sufficient evidence in the radiograph to detect infection. It often happens that the systemic damage is being done in this period when x-ray evidence is still negative.

In the presence of serious systemic disease of focal origin all pulpless teeth should be under suspicion until proof of innocence can be adduced.

CASE II RECURRENT IRITIS FROM RESIDUAL INFECTION IN THE JAW

Case History—F W P, a farmer, age forty-two, stated that he had had an attack of arthritis involving the hip-joints in 1916. The left temporomaxillary joint had been painful for eighteen months and the costochondral articulations for one year. The patient's particular complaint was recurrent attacks of iritis. The first had occurred in 1915 and involved only the left eye. The tonsils were removed at that time, with some improvement in the eye condition. The iritis recurred in three weeks. An impacted molar tooth and a crowned tooth were extracted. The eye infection had recurred at irregular intervals. In July, 1922 the patient had an attack of iritis in the right eye for the first time followed by a second in July, 1923, when I first saw him. In 1921 the patient, in desperation, on his own initiative, had had all filled teeth removed, although these were vital.

The patient was in an excellent state of nutrition. He presented the typical signs of an acute iritis in the right eye. The tonsils had been cleanly removed. The Wassermann test

was negative. The radiograph showed no pulpless or filled teeth. However, there was a large area of rarified bone containing a small sequestrum at the site of extraction of the upper left first bicuspid. This tooth had been extracted in 1916. A radiograph taken just before the extraction showed no bone absorption about the root (Fig 184, *a*). The root canal was

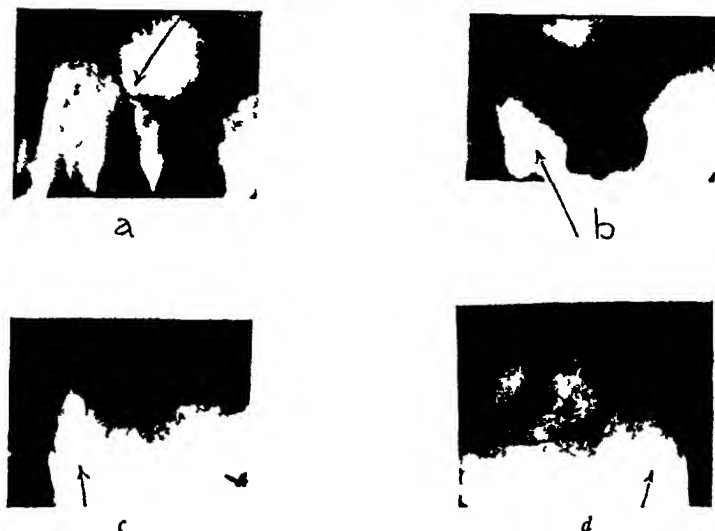


Fig 184—*a*, Radiograph of bicuspid tooth of a patient suffering from recurrent iritis taken in February, 1916. The tooth was extracted at this time. *b*, Area of rarified bone at site of extraction of the extracted tooth. This radiograph was taken in September, 1918. *c*, Radiograph of the same area taken in July, 1923. The area is larger and a sequestrum is present. At operation this area was very soft and a culture showed a profuse growth of a non hemolytic streptococcus which produced iritis in rabbits. *d*, Same area in September, 1923, showing regeneration of bone.

poorly filled. A second picture of this area taken in 1918 showed rarified bone (Fig 184, *b*). This condition was much more marked in the radiograph taken in July, 1923 (Fig 184, *c*).

This area when exposed was found to be very soft. Curettings showed a profuse growth of a short chain streptococcus. Two rabbits injected with the streptococcus developed a marked bilateral iritis. Following the curetting of this area the patient

developed a severe iritis in the left eye which had been free from infection at the time of operation. The left temporo-maxillary joint also became very painful. When last seen in September, 1923 the right eye was normal and the left eye had almost recovered. A radiograph taken at this time showed good bone regeneration in the affected area (Fig 184, *d*)

Discussion—This case illustrates something which is often neglected in the search for foci of infection. It is not at all uncommon to find areas of infection remaining at the site of extraction of infected teeth. These areas represent points of latent, smoldering, or active infection. Often a part of the granuloma at the apex of a tooth is left behind or diseased bone remains. The gum heals over, leaving these areas to act as a foci of infection.

The fact that the patient's infection flared up following the curetting of this area and that animals injected with the organism recovered developed iritis seems most suggestive evidence of the causal relationship of the infection to the systemic manifestations.

Too often the possibility of infection about the jaws is considered eliminated because the patient is edentulous. Frequently we have patients present themselves with radiographs in which no films are included of those areas from which teeth have been extracted. The point cannot be too strongly emphasized that in looking for foci of infection complete radiographs of the jaws including all areas from which teeth are missing should be taken.

CASE III ONYCHIA FROM MULTIPLE FOCI OF INFECTION

Case History—C S, a maid, age thirty-one, complained of trouble with her finger-nails. She had had attacks of iritis four and five years ago. Three years previously she had had two attacks of pyelitis. She stated that there had been some swelling and redness around the nail of the right middle finger for a long while. Four weeks before admission the thumb of the right hand had become similarly involved following the attempted extraction of an infected tooth.

The examination showed marked swelling and redness around the nail of the thumb and middle finger of right hand. No pus could be expressed. The blood-count was normal and the urine examination was negative. The Wassermann test was negative. Radiographs showed many pulpless teeth. Several rabbits were injected with the organisms recovered from



Fig. 185 —Forefeet of rabbit injected with the bacteria isolated from the infected teeth of a patient with multiple onychia. Note the marked swelling around the nail root of index finger on right as contrasted with the normal index finger on left.

the extracted teeth. Several showed marked involvement of the nail (Fig. 185).

The production in animals of such a highly specific lesion as an onychia left little doubt that the infected teeth were a factor in the nail lesions. The patient did not, however, recover as one would expect if the causative factor were removed properly.

The tonsils were large and red. Frank pus could be expressed from the crypts. A pure culture of a green-producing streptococcus was obtained from the tonsils. A rabbit injected with the organism developed marked involvement of the nails similar to that produced by the bacteria from the teeth.

Discussion—It is very common to find that the clinical manifestations of focal infection are due to more than one focus as is illustrated by this patient's history. In the presence of several possible foci one can never be sure of just how many are taking part in the production of the systemic disease. All possible foci should be eradicated if a patient is suffering from serious metastatic disease of focal origin. Just how far one should go in the removal of possible sources of infection depends upon clinical judgment in the case at hand. One should be sure first of all, if such be possible, that the lesion which the patient presents is of focal origin. If the lesion is not a serious one, possible areas of infection may be allowed to remain and be watched in the hope that the infection will be overcome. Such a course should not be followed in the presence of a serious systemic condition.

CASE IV RECURRENT PEPTIC ULCER FROM A SINGLE FOCUS IN THE PRESENCE OF MULTIPLE FOCI

Case History—W. T. G., business man, age forty-three, complained of a "dull, burning sensation" in his epigastrium in October, 1922. The trouble came on from one-half to two hours after meals and was relieved by food or soda. Frequent heartburn. No acute pain or vomiting. The examination was negative except for tenderness at the tip of the ninth rib in front and several pulpless teeth. The tonsils had been removed. The patient became free from symptoms on a special diet until April, 1923, when he presented the typical symptoms of a duodenal ulcer. An Ewald test-meal showed free HCl, 40 acidity per cent, and total acid, 65 acidity per cent. The radiographic examination showed marked deformity of the duodenal cap. The symptoms again disappeared under treatment.

Radiographs of the teeth at this time showed three pulp-

less teeth with root canals completely filled. All had some bone absorption around the root tip. The three teeth were ex-



Fig. 186—Radiograph of lateral incisor tooth (indicated by arrow) the injection of the culture from which produced the gastric lesions shown in Fig. 187. The adjacent tooth was also heavily infected, but produced no lesions in animals.

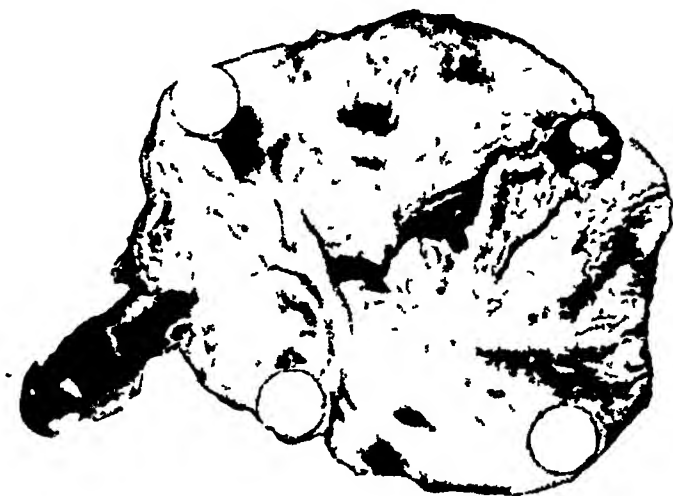


Fig. 187—Stomach of rabbit twenty-four hours after injection (intravenous) with the culture of the organism from the tooth indicated by arrow in Fig. 182. Note the multiple hemorrhages in mucosa and actual ulceration in certain areas.

tracted. Cultures of all in deep tubes of glucose-brain-broth-agar showed many colonies of bacteria.

Two rabbits were injected with the broth culture from each tooth. Two animals showed no lesions anywhere and two only purulent fluid in the larger joints. The two rabbits injected from the culture from the upper right lateral incisor (Fig 186) died the day following the injection. There were many hemorrhages in the gastric mucosa some of which had progressed to ulceration (Fig 187). Three other animals were injected with the same organism in doses down to 0.5 c.c. All showed at autopsy hemorrhages in the gastric mucosa.

Discussion—This patient had three pulpless teeth all of which were proved to be heavily infected by culture. Injections from two cultures produced no lesions in animals. All animals injected with the third culture showed lesions in the stomach. These findings suggest that only one tooth was responsible for the systemic disease. It is probable that it is true in many cases that the clinical manifestations arise from a single focus even when multiple foci are present. Rosenow has emphasized the fact that a focus of infection not only provides a point for the harboring of bacteria but also affords proper conditions for the acquirement of those characteristics which determine affinity for certain tissues. This affinity is probably largely an adaptation to a certain oxygen tension.

CONTRIBUTION BY DR GEORGE HOWARD HOXIE

RESEARCH HOSPITAL CLINIC

THE DIFFERENTIAL DIAGNOSIS BETWEEN BEGINNING OR LOW-GRADE HYPERTHYROIDISM AND THE EXHAUSTION OF THE BODY DUE TO FOCAL INFECTIONS

Case I—The chief complaint of the patient (C J H) is nervousness. This started in 1919 and manifested itself chiefly in the form of palpitation. This palpitation is more evident after meals than it is after exertion.

He has had various diagnoses. In accordance with one of them he spent at least a month in a sanitarium for tuberculosis at Colorado Springs. Another attributed his trouble to leakage of the heart, and he was put to bed on that score. But no diagnosis has resulted in a satisfactory line of treatment, and he comes in now to have the situation cleared up.

His height is 5 feet, 10 inches, standard weight 150 pounds, present weight 134 pounds.

His appetite is poor, his bowels constipated, sleep poor. He has some nocturia. He states that there is pain in the frontal region over his eyes after exertion.

The blood examination gave hemoglobin 95, with red counts varying from 4,960,000 to 6,200,000. The whites varied from 6200 to 11,800.

The urine is abundant, with low specific gravity, a trace of albumin, but no casts. Occasionally it shows indican.

The phthalein renal function test showed 25 per cent. in the first hour and 12 per cent. in the second. A later test gave 32 per cent. the first hour and 25 per cent. the second.

His basal metabolic rate ran always within normal limits—plus 8, plus 3, minus 9.

The Goetsch adrenal test was negative.

The blood-sugar tolerance gave readings of 09, 163, 128 09

The blood-pressure was low, varying from 96 and 118 to 76 and 110

The x-ray study of the digestive tract showed sluggish peristalsis with an initial pyloric spasm. Manual manipulation caused the pylorus to open. The stomach was four-fifths empty in three hours—entirely so in five hours. The x-ray study of the head showed a slight clouding of the right ethmoid area and an enlarged posterior clinoid of the sella turcica. The nasal septum was deviated and the lower turbinates hypertrophied.

The examination of the nose by a rhinologist found that aside from the condition of the nasal cavities there was nothing to require surgical interference. The throat showed inflamed tonsillar rests. These were removed and cultures made which showed diplo-streptococci.

The stomach contents were negative except for low free hydrochloric acid.

The Wassermann was negative.

The highest pulse was 100, the highest temperature was 99.2° F.

Comment. At first blush there seemed to be three possibilities in this case—tuberculosis, beginning hyperthyroidism, and some type of nervous exhaustion from focal infection.

In favor of tuberculosis is the slight rise in temperature, the complaint of weakness, the history of cough and yellow sputum. However, the temperature disappeared on bed rest, the weakness persisted, the cough disappeared on bed rest and the sputum did not show any tubercle bacilli. Moreover, the x-ray plates were startlingly clear and free from evidence of disease.

In favor of beginning hyperthyroidism are the weakness, the nervousness, and the general upset of the intestinal tract. These factors cannot be ruled out easily, but against them are the results of the basal metabolism and the blood-sugar tolerance tests. In fact, this has seemed to most of the physicians who have seen the case as the plausible explanation of his condition. But prolonged observation has demonstrated the absence of any

authentic signs indicating the overactivity of the thyroid gland. The gland itself is not palpable. There is no increase in the metabolic rate. There is no increased pulse-rate. There are no tremors. There is no exophthalmos. There is no adrenal sign. In fact, so sure were we as a result of the examination that the condition was not due to hyperthyroidism that we made a therapeutic test and administered thyroid extract without any change in the symptomatology.

There remains only the possibility of neurasthenia following focal infection. The only focus found was the tonsillar remnant. We removed this and the patient began immediately to put on weight. The reaction to the vaccine made from the tonsillar bacteria was so sharp as to indicate a previous sensitization to them.

An interesting side-light on the case is given by the action of the kidneys. They have secreted from 110 to 138 ounces of urine daily, with only slight evidence of renal disease. The phthalein renal function test has improved following the stay in the hospital. This also offers some slight evidence in favor of there having been at the beginning a focal infection and that the kidneys had been slightly injured by it, but that this injury is being overcome by the relief from the initial lesion.

The treatment of such cases is rather unsatisfactory because it demands the fulfilment of three requirements. First the removal of the original focal infection, second, the stimulation of the functions of the body, and third, a rest so prolonged that the machinery of the body may be restored to its rhythm. Consequently, one has to acknowledge at the onset that his success would depend to a large extent on the reaction of the patient himself. If the patient has moral stamina and determination, he will probably beat his way back to normalcy.

Case II—Frequently the differential diagnosis is more complicated, as in the following case.

Female (G. W.), age twenty-nine, stenographer. Her chief complaint is dysmenorrhea, leukorrhea, delayed menstruation.

The examination of this patient showed that she had fibrous

changes in the lungs, especially about the right apex, that the teeth were poor, that there was a systolic bruit over the base of the heart and enteroptosis, that the uterus was small and fixed to the back and left, with an atrophic cervix

The urine was negative except for increased acidity and a trace of sugar

The blood showed Hb 80 per cent, with 4,000,000 reds, 6400 whites, and 64 per cent polys

The B M R in this case was minus 2 The blood-sugar reading was 06, 084, 12, 13 The urine was sugar free

Her temperature, however, was nearly always 99° or 99 2° F

This patient's weight was down to 91 pounds, her best weight having been 104 pounds The blood-pressure ran 80-128 and the pulse in the 90's (88-96) The patient quit work and was sent home and slept well and rested, with the result that she gained about 7 pounds in weight and the temperature became normal

When next seen the throat showed a nasopharyngitis The right apex of the lung still showed the prolonged expiration and increased whisper The heart was negative As a result of the death of her father the patient was compelled to give up her rest cure and go back to work After some weeks of work she showed digestive disturbances. The total acidity after a full meal was 78 and the free HCl was 33

At present the B M R is minus 3, the temperature 98 2° F, pulse 64, blood-pressure 80-128 The blood-sugar tolerance shows 103, 15, 194, 14, and sugar appears in the urine one hour after the ingestion of the glucose Her weight has dropped back pretty much to what it was a year ago

Here we have the evidence of incipient tuberculosis and added to it the presence of a focal infection in the nose and throat. The effect on the B M R was nil, but the effect on the blood-sugar tolerance was to decrease it

In other words, there seems to be a point in the differential diagnosis between hyperthyroidism and focal infection in the evidence presented by the calorimetric test and blood-sugar tolerance test That is, we are finding that hyperthyroidism is ac-

accompanied by a definite increase in the metabolic rate and that a decrease in the sugar tolerance is a regular sign of focal infection

Henry John, of the Cleveland Clinic, has taken the position that glycosuria and the so-called diabetic blood-sugar curve indicate a damage to the pancreas. But our work would rather indicate that if the pancreas has been damaged at all, it has been only slightly so, and that it recovers from such injury whenever the body as a whole recovers from its exhaustion. We are rather of the opinion that the appearance of sugar in the urine under conditions of the blood-sugar tolerance test point toward an exhaustion that is probably due to the presence of focal infection.

Case III —(W E B) Male, thirty-one years of age, married, 2 children. So completely knocked out that he has had to give up work. Nervousness is the predominant factor, but there is also a pain in the back and some neuralgia. There is pain in the left lower quadrant of the abdomen which extends downward into the testes. There is history of blood in the stools and of a bloody discharge from the tonsils.

The past history shows that he had "walking typhoid" in 1912, mumps and orchitis in 1912, "typhoid" in 1914. In 1918 an attack of insomnia with pain (from which he fainted) in the lower left quadrant. No vomiting. Again in 1921 he had pain in the right side. In October, 1922 he had tonsillitis followed by a tonsillectomy. He attributes the present attack to eating a pound of peanuts in November, 1922, because he has never felt well since.

The examination developed the following interesting points. His blood-pressure was very variable and not sustained. It differed from right to left and from moment to moment. His hands were cold and bluish. The tonsillar fossa showed the scarred bases of the tonsils. The apex of the right lung showed a harsh respiration, but no râles. The skin showed dermatographia. The urine was negative.

The B M R was minus 1 per cent. The figures on the blood-

sugar tolerance test were 104, 128, 18, 138, and sugar appeared in the urine one hour after the ingestion of the normal amount of glucose

The blood showed Hb 95 per cent red blood-corpuscles 5,000,000, white blood-corpuscles 6000, granular cells 60 The coagulation time was much delayed

After the examination and a slight massage of the vesicles the urine showed considerable blood and blood-cells

This patient on first appearance would be classified as a thyroid case In favor of the hyperthyroidism is the weakness, the nervousness so great that he could not attend to his work, and a loss in weight

These things might also speak for tuberculosis But against tuberculosis is the fact that he had no fever, no cough, and although he did have night-sweats, there was nothing to point to the lungs as the source of the trouble

In favor of focal infection was the condition of the throat and the condition of the vesicles

He evidently is an example of status thymicolymphaticus, and had he been in the military service would probably have been marked down as an example of neurocirculatory asthenia

The interesting thing about the case is the result of the milking of the vesicles Almost immediately he lost his backache, his indigestion, and signs of intoxication He began to put on weight, his blood-pressure became steady, and his self-confidence returned

Case IV—A young man (R L T) of twenty-seven, married, 1 child office worker, has been working steadily for several years without any evidence of disease, broke down in December 1922, with sensations of faintness palpitation of the heart nervousness, belching after meals

Weight 137 pounds, normal 150 to 153 pounds Appetite, bowel action, urination, and sleep negative

The examination showed hardened and hypertrophied tonsils, carious teeth, and some gastric succussion Blood-pressure 80 135

The urine showed a trace of albumin otherwise negative

The blood showed Hb 90, red blood-corpuscles 4,640,000, white blood-corpuscles 9000, granular cells 71

The B M R was plus 10 The blood-sugar figures were 126, 28, 164, 137 with sugar appearing in the urine at the half-hour and the hour periods only

The gastric contents showed a large amount of mucus with 50 points of free HCl, total acidity of 100, one hour after a test-meal The fasting stomach contained 50 c c of a mucous fluid tinged with bile which showed a free HCl of 40 points and a total acidity of 50 The gastric contents stood in three layers—first, bile tinged, second, plain mucus, third, bile

The Rehfuß tube showed that the pylorus was open, and in the tetrachlor test the dye appeared in eleven minutes

This young man had quit work in December and had been trying to secure relief by taking a great deal of exercise in the open air, and trying to force himself to be better—evidently on the theory that he was a neurasthenic and simply needed a change of work

In this case his long sighing respiration the sensations of faintness, the palpitation, the nervousness made one think of the cases of persistent thymus And it was with a great deal of interest that we worked out the B M R This was plus 10, just on the borderline between normal and the abnormal With the slight increase in the metabolism it would be unexpected to find the thymus overactive

When, then, the blood-sugar tolerance showed a great decrease it became evident that we are dealing not with a thymic case nor yet with a hyperthyroid case, but rather one due to focal infection

In this case there arose the interesting point as to whether the gastric succussion indicated some gastric disorder as the cause, or was simply due to the weakness from systemic exhaustion

The result of removing the teeth and tonsils and of putting the patient to bed on a restricted diet was so good that it proved that his case was one of focal infection rather than of endocrine disturbance

Conclusions —From a review of such cases one cannot resist the conclusion that the calorimetric test is essential before one diagnoses such borderline cases as due to endocrine disorders.

A second conclusion is that the appearance of sugar in the urine after the ingestion of a standard amount of glucose (15 grams per kilogram of body weight) indicates an exhaustion of the resistance of the body (such as might be found in cases of focal infection) rather than an endocrine upset *per se*.

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THE EFFECT OF HIGH FAT FEEDING IN DIABETES

IN 1796 John Rollo, a surgeon in the English Army, attempted to revolutionize the treatment of diabetes. He believed diabetes to be a disease of the stomach, characterized by an increased secretion of an abnormal gastric juice, which, in turn, apparently had to do with the formation of sugar from the various foods ingested. He held that saccharin was formed in the stomach chiefly from vegetable matter, and concluded that to properly treat diabetes the source of sugar must be dispensed with. Therefore he advocated, as nearly as possible, a diet limited to animal products with the addition of drugs which would produce anorexia and nausea, or in general would cause retardation of the activity of the stomach. Antimony, ammonium sulphid, digitalis, opium, rancid fats, and tobacco being his favorites. The results were so startling as to produce worldwide comment.

His first patient, an army captain, was treated as follows. Patient was confined to bed with utmost quiet and absolute avoidance of exercise. His diet was

Breakfast $1\frac{1}{2}$ pints milk with $\frac{1}{2}$ pint lime-water, 1 slice bread with butter

(Noon Plain blood pudding, made of blood and suet

Dinner Game or old meats, which had been long kept, and as far as the stomach would permit, fat and rancid old meats, such as pork

Supper Same as breakfast

His watchword was to eat in moderation. Such a diet was not relished by Rollo's patients, and they soon rebelled at the mere sight of greasy foods, and ate only enough to sustain life

Thus, unbeknown to the author, we have the first introduction of two important elements in diabetic treatment—undernutrition and high fat feeding.

Since Rollo's time numerous investigators have attempted to control the symptoms of diabetes and at the same time to maintain body weight by diets low in carbohydrate and protein and high in fat. These attempts have met with more or less failure. Consequently Allen's classical contribution of undernutrition was eagerly accepted and certainly proved to be one great advance in modern diabetic therapy. He pointed out that while fat was the principal article of diet that was available for use in diabetes, that excesses in fat always were associated with liberation of acid bodies. His classical experiments on partially depancreatized dogs, fed diets high in fats, are, to my mind, conclusive. Dogs that were able to maintain a fair existence on beef lung were given, in addition, varying amounts of suet, with the result that they at once improved. Their coats became sleek and they were much more alert, but they soon developed glycosuria and acidosis, lost weight, and in general developed into fatal cases. No dietary restrictions could restore the carbohydrate tolerance they enjoyed before the excessive fat was added to their diet. His cases—No. 34, a boy, and No. 66, a girl—described in the monograph are of interest. Both were considered of equal severity. The boy was treated along orthodox lines. He was allowed high caloric rations, presumably suitable for his age. His weight was maintained, but his blood-sugar remained high. The boy developed coma and died eleven months after his admission, two years after onset. This line of treatment has in its favor a feeling of well being and comfort, but certainly is not conducive to long life. The girl was dismissed weighing 5 kg. less than at admission and has kept underweight since. This patient was living and symptom free over two years after dismissal from the hospital.

Joslin, who probably has had a larger experience than any other observer in this country, agrees entirely with Allen's hypothesis and is possibly more insistent on the harmful results of fat. Until some method of general treatment proves superior,

by actual case records over a long period of time, we are justified in accepting Joslin's statistics as accurate

Recently Newburg and Marsh have reported a series of cases fed on diets high in fats, with brilliant results. They introduce a new idea of endogenous and exogenous metabolism, insisting that patients who are undernourished will metabolize their own body tissues, and that from a purely metabolic standpoint little or no difference is encountered between body and food fat.

Leprn, working independently, arrives at similar conclusions.

Leclercq, basing his conclusions on fewer, but possibly more thoroughly controlled cases, fails entirely to corroborate the findings of Newburg and Marsh.

Allen, commenting on the results of Newburg and Marsh and Leprn, feels that their results are hardly fair, in that most of their cases are not truly severe in the light of classifications followed by most investigators today.

Woodyatt, Wilder, Schaffer, and others have attempted to simplify the subject and have offered formulæ by which proper diets might be calculated for any given patient. These formulæ with individual variations are supposed to satisfy two metabolic requirements. First, that the ratio of available ketogenic compounds to carbohydrate must be within certain limits, namely, from 1.5 to 2.5 to 1.

Woodyatt has demonstrated that in completely diabetic animals foods are metabolized as follows:

Carbohydrates as 100 per cent glucose

Protein as 58 per cent glucose—46 per cent higher fatty acids

Fat as 10 per cent glycerol (glucose)—90 per cent higher fatty acids

Second, that the total caloric value of the ration shall be in keeping with established metabolic requirements based on body weight, height, age, and body surface.

To me, the weakness of such formulæ lies in the fact that they fail to provide for individual metabolic variations. I have some diabetic patients who maintain weight on 25 calories and

others who lose weight on 35 calories per kg body weight. I also have some patients who have done well for over a year on diets relatively high in fat, and, on the other hand, I have several who are in apparent metabolic equilibrium and will develop glycosuria and mild acidosis with an increase of 100 to 150 calories in the form of fat.

The present paper deals with an attempt to provide a method whereby we can determine in individual cases which ones will tolerate high fat diets and those cases in which diets rich in fat might be injurious.

If we assume that all the carbohydrates and 58 per cent of the protein in the diet is metabolized as glucose in every individual case, our problem will be simple and can be solved entirely by arithmetic. I propose to show by blood-sugar curves following standard protein meals that all diabetic patients do not metabolize protein in a constant manner, and that, therefore, formulæ which do not control these individual variations are not adequate.

Jacobsen and Edwards find that diabetics constantly show increase in blood-sugar after protein meals. Rolly and Offermar find a rise of blood-sugar after protein meals in some diabetics. Mosenthol, Clausen, and Hiller find that carbohydrate-free meals produce hyperglycemia in some diabetics, especially those with low fasting blood-sugars, and they think that in those cases with high fasting blood-sugars the rise is simply masked.

All observers agree that no appreciable rise in blood-sugar is found in normal persons after protein meals.

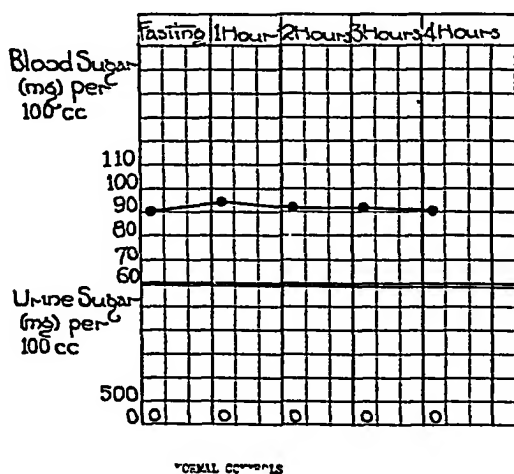
The following method was used in our series. The patients (usually under treatment) presented themselves at the laboratory in the morning without breakfast. Samples of blood and urine were taken and the patients were given 185 gm chopped beef. They were allowed water freely. Samples of blood and urine were taken at one-hour intervals for four hours. Determinations of sugar, urea nitrogen, non-protein nitrogen, CO combining power of the plasma and chlorids were made in

the blood samples and sugar and non-protein nitrogen in urine samples

Figure 188 represents normal persons

Figure 189 represents 10 diabetic cases whose sugar curves showed no definite elevations

Normal Controls — 4 Cases



Case No.	Sex	Age	Height	Weight	Blood					Urine				
					fast	1	2	3	4	fast	1	2	3	4
2-9	normal	43	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0
4-72	normal	25	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0
4-72	normal	25	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0
4-72	normal	25	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0
4-72	normal	25	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0
4-72	normal	25	5'8"	143	85	104	104	118	111	0	0	0	0	0
	1.0/85	max	1.43	143	85	104	104	118	111	0	0	0	0	0

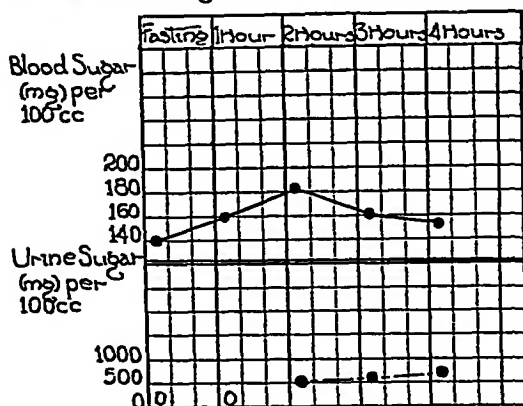
Fig 188

Figure 190 represents 15 cases whose sugar curves show definite high elevations

Group II Of these 10 cases, 1 had a positive Wassermann test, 5 had definite arterial hypertension, 1 with nephritis, therefore, we will include only 4 cases for comparison

Case No 14,626 Severe—emaciated—eight months' dura-

15 Cases showing definite elevation in curve



15 CASES SHOWING DEFINITE ELEVATION IN BLOOD SUGAR CURVE

Case No.	Sex	Age	F	Ave. Rate	Height	Weight	Blood					Urine				
							fast	1	2	3	4	fast	1	2	3	4
11019				moderate	35	119	182	200	230	260	275	76	42	41	58	1
				moderate	35	119	182	200	230	260	275	76	42	41	58	1
2995				moderate	45	174.5	23	23	25	32	42	64	9	19	19	64
				moderate	45	174.5	23	23	25	32	42	64	9	19	19	64
Enery Cox				moderate	40	140	110	134	155	178	169	63	63	64	63	73
				moderate	40	140	110	134	155	178	169	63	63	64	63	73
St JO B W				moderate	42	177	127	154	178	200	210	72	63	63	63	63
				moderate	42	177	127	154	178	200	210	72	63	63	63	63
25711				moderate	47	148	135	155	178	200	210	37	63	63	63	63
				moderate	47	148	135	155	178	200	210	37	63	63	63	63
223				moderate	42	140	116	134	155	178	200	72	63	63	63	63
				moderate	42	140	116	134	155	178	200	72	63	63	63	63
23448				moderate	46	140	116	134	155	178	200	72	63	63	63	63
				moderate	46	140	116	134	155	178	200	72	63	63	63	63
22				moderate	42	140	116	134	155	178	200	72	63	63	63	63
				moderate	42	140	116	134	155	178	200	72	63	63	63	63
193				moderate	41	140	116	134	155	178	200	72	63	63	63	63
				moderate	41	140	116	134	155	178	200	72	63	63	63	63
2772				moderate	42	140	116	134	155	178	200	72	63	63	63	63
				moderate	42	140	116	134	155	178	200	72	63	63	63	63
2110				moderate	40	140	116	134	155	178	200	72	63	63	63	63
				moderate	40	140	116	134	155	178	200	72	63	63	63	63
23				moderate	44	140	116	134	155	178	200	72	63	63	63	63
				moderate	44	140	116	134	155	178	200	72	63	63	63	63
3/3				moderate	44	140	116	134	155	178	200	72	63	63	63	63
				moderate	44	140	116	134	155	178	200	72	63	63	63	63
Self				moderate	42	140	116	134	155	178	200	72	63	63	63	63
				moderate	42	140	116	134	155	178	200	72	63	63	63	63

tion Was kept sugar free with difficulty on a diet of C-15, P-35, F-40 She developed glycosuria and acidosis regularly on an increase of 10-15 gm fat

Case No 25,280 Severe—emaciated—duration six months Was able to keep sugar free on a diet of C-10, P-30 F-40, with one fast day per week She developed glycosuria and acidosis with the addition of 10 gm fat We made arrangements for her to enter the hospital for treatment with insulin, but she died in coma the day before she was to come to the hospital This patient, as subsequent experience with insulin has shown, would have been saved

Case No 9584 Moderately severe—emaciated—duration two years Gained a tolerance of C-36, P-60, F-90, but was unable to tolerate fat in excess of this amount without glycosuria

Case No 12,712 Severe—emaciated—duration six years Finally became sugar free and free from acidosis on a diet consisting of C-20, P-60, F-70, with higher fat he invariably developed glycosuria, but no acidosis

These cases were all in nitrogen equilibrium and therefore burned little or no body protein, a fact somewhat surprising because they were all emaciated None of them were able to tolerate fat even in amounts covered by Woodyatt, minimum namely, $F = C_2 + \frac{P}{2}$

Group No III Of these cases 2 had positive Wassermann tests Four had arterial hypertension, some with varying degrees of renal insufficiency and were not included

Case No 28,180 Severe—emaciated—duration one year Occasional nitrogen balance, acquired a tolerance of C-40, P-9, F-125, which was within the limits of Woodyatt's formula, however, we attempted to increase her fat, with the result that her metabolism was so injured that she has never been able to maintain more than a very low caloric diet since On March 3d her diet was C-30 P-50 F-70 She had 182 mg blood sugar and 3.9 per cent urinary sugar, with diacetic acid and acetone positive

Case No 11,019 Moderate emaciated—duration seven

years Attained a tolerance of C-40, P-70, F-115 She has remained symptom free since

Case No 29,711 Mild—obese—duration two years Was able to eat fat far in excess of Woodyatt's formula She, however, was given a rather low caloric diet, by which she lost 10 kg, and has been in carbohydrate and nitrogen balance since

Case S G Moderate—normal weight—duration two years Easily developed a tolerance of C-40, P-70, F-125 She is in perfect carbohydrate and nitrogen balance

Case No 26,880 Moderately severe—emaciated—duration one year Had gangrene in right foot Became sugar free with normal blood-sugar in forty-eight hours and soon developed a tolerance of C-50, P-70, F-145 On several occasions he was given additional fat in 10- and 15-gram amounts with apparently no immediate harm He left the clinic in perfect carbohydrate and nitrogen balance, his foot having healed He re-entered the clinic some two months later feeling good, and upon examination we found him to be in carbohydrate and nitrogen with a blood-sugar of 125 mg

Case D M Moderately severe—emaciated—duration six months Was made sugar free in thirty-six hours by partial fasting and easily developed a tolerance of C-40, P-70, F-140, however, he would occasionally develop slight glycosuria and lost weight rather rapidly His blood-sugar remained relatively low Weekly fast days were instituted and in six weeks he had developed a tolerance of C-50, P-70, F-165, which diet he maintained for five months Occasionally he would come into the hospital for observation, and each time I would increase his fat by 15-20 gm during his stay On January 22d his blood-sugar was 120 mg, CO₂ combining power of blood plasma 51 vol per cent, and he had been on a diet for the previous two months of C-60, P-70, F-175 At times his nitrogen balance was negative, but he never has had a negative carbohydrate balance

Case E C Severe—juvenile—emaciated—duration three months Developed a tolerance of C-25, P-40, F-65 He would not adhere strictly to diet and we were unable to report ac-

curately on his case. He was given insulin during his stay in the hospital, and we were unable to even ascertain definitely the effect of insulin. It might be of interest to note that in seven of these patients Armour's insulase has been used with absolutely no result, except Case D M.

In fact some cases (Case 11,019, D M, 28,180-8091, and 12,639) have actually lost ground. On the other hand, cases under insulin unquestionably gain tolerance and improve generally.

Some interesting facts are brought out in a study of these cases

- 1 Those cases who fail to respond to protein meals with elevated blood-sugar curves apparently have no difficulty in maintaining a normal nitrogen balance. They do not tolerate even a moderate amount of fat.

- 2 Those cases who respond to protein meals with a definite elevation of blood-sugar are prone to burn their body protein. They tolerate diets relatively high in fat, although in this some have failed to exceed to any appreciable degree fat rations in excess of that calculated from Woodyatt's formula.

- 3 The apex of the sugar curve following protein meals is delayed usually to the third hour, unlike the glucose tolerance curve in which the apex occurs during the first hour.

CLINIC OF DR LOGAN CLENDENING

OUT-PATIENT DEPARTMENT, BELL MEMORIAL HOSPITAL,
UNIVERSITY OF KANSAS

EXAMPLES OF INTESTINAL INVALIDS

THE patients which I wish to examine and consider with you this morning have all had some form of intestinal disturbance, though in every instance I believe it to be functional or only partially organic in nature. My especial reason for presenting them is to call your attention to the value of a patient consideration of the history and a thorough trial of the methods of examination available in such cases. Too often, it is to be regretted, these patients seek medical advice only to be somewhat abruptly dismissed with a routine and thoroughly perfunctory prescription. They seldom need medicine. What they do need is care, thought and common sense, instruction in diet, and in rules of living.

CASE I. CONSTIPATION

This woman, aged thirty-two, stated a week or two ago that she never had a natural bowel movement, that she had taken a cathartic every night for ten years, and that when she did not she was thoroughly miserable and felt stopped up and head-achy.

Physical examination was practically negative. She was not undernourished. There was no abdominal tenderness. A single examination of the gastric contents after a test breakfast showed the amount and proportions of the secretion within normal limits.

A sigmoidoscopic examination showed a normal appearing rectal mucosa.

We then resorted to a procedure which has been very valuable in these cases—the study of a barium meal from the time of its ingestion to the time of its leaving the gastro-intestinal canal. The radiologist sent us three plates—one taken immediately after ingestion, one twenty-four hours later, and one forty-eight hours later. The important thing in this case was that at the end of the forty-eight-hour period all traces of barium had left the gastro-intestinal canal. The patient had taken no cathartic during the examining period. There was then a perfectly normal time interval for a complete evacuation of the bowels.

We instructed the patient to abstain entirely from the use of cathartics. She was told to drink a glass of water on arising, and to eat a dish of bran every morning for breakfast, and twice a day to give herself mild abdominal massage while in the defecation posture.

We also asked her to keep a record of the bowel movements, each day, and bring the record to us. At the end of a week on this routine she gave us the following record:

Day	Number of bowel movements
— Sunday	1
Monday	1
Tuesday	0
Wednesday	2
Thursday	1
Friday	1

She had taken no cathartics whatever and was herself astonished at the result.

Cases of this kind represent about 30 per cent of the cases of chronic constipation applying for relief. They have no actual constipation at all. They have dosed themselves with cathartics for years more from a dread of what might happen than from actual necessity. The bowel is often so inured to the presence of cathartics that in many cases it takes some weeks to re-establish a normal defecation cycle.

The psychology of such patients is interesting. They have become, in many instances abnormally apprehensive of the

dangers of constipation They force on themselves all manner of symptoms—melancholy, fatigue, etc—which they ascribe to the constipation and which are almost entirely psychogenic The more I see of constipation the more I am impressed with the general harmlessness of it. It is significant to see the accounts from all centers of psychic therapy, the Christian Scientist, and M. Coué, etc., of cures of constipation from mental treatment alone These cases must belong, largely, to the same group as this patient

CASE II CONSTIPATION, SPASTIC IN TYPE, WITH INFLAMMATORY DEPOSITS IN THE MUCOSA

The patient, a man of forty-eight years, has taken cathartics regularly for many years He is a druggist and has used a large variety of these drugs His favorite and most often used one is compound glycerhiza powder, taking as much as he can get on the end of a knife-blade

He sought advice following a rather acute abdominal crisis He was seized one morning while at work with severe left-sided abdominal cramps He was compelled to sit down and double up While in this position he saw his face in a mirror and was alarmed at his appearance He said he looked like a person in shock The features were pinched, and the whole face leaden gray in color Later he fainted, and when coming out of this faint he vomited After he began to feel better, under the impression that he needed a good cleaning out of the bowel, he took a large dose of salts, but found that this brought about an alarming recurrence of his abdominal pain and his faintness

Upon my advice he went to bed for a few days, and took one or two soapsuds enemata He also used hot compresses on the abdomen On this routine he felt much better

The sigmoidoscopic examination of this man was instructive It was noticed that the sphincter, the rectum, and the sigmoid closed tight over the instrument and almost could be said to grasp it, in an effort to prevent its introduction The sigmoid

mucosa was red, congested, and covered with punctate spots of hemorrhage and inflammation

For treatment I employed a method introduced by Dr Horace W Soper, of St Louis A powder consisting of equal parts of bismuth subnitrate and calomel was blown into the lumen of the bowel through a sigmoidoscope The powder coats the surface of the mucosa, as Dr Soper says, "like the frosting on a cake," and acts as an antiseptic and anti-irritant This was done on alternate days On the other days a 50 per cent

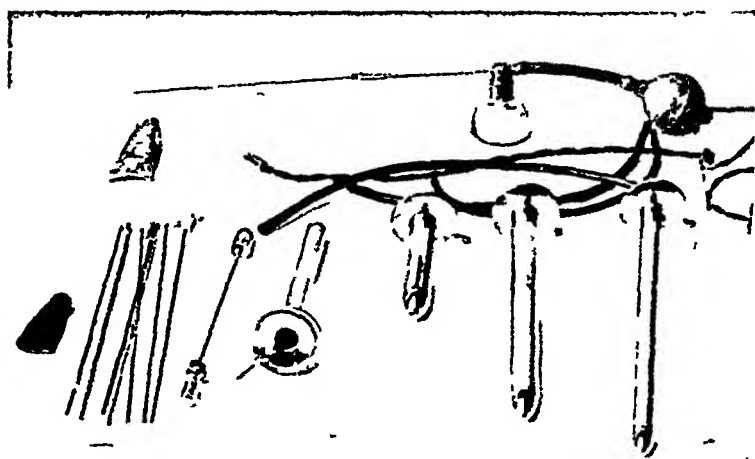


Fig 191—Table arrangement for sigmoidoscopic examination and treatment Note graduated size of diameter as well as length of sigmoidoscopes Powder blower with long nozzle for application of bismuth and calomel to rectal mucosa Method of Dr H W Soper

solution of magnesium sulphate was introduced into the sigmoid colon through a catheter and left there This acts as does magnesium sulphate everywhere on the surface of the intestinal mucosa as an antispasmodic For this patient cathartics were absolutely interdicted Recovery was rapid, and with some periodic recurrences, the constipation has been greatly improved

This case is an example of spastic constipation largely due to the habitual use of cathartics

CASE III MUCOUS COLITIS DUE TO SIGMOID DIVERTICULITIS

This man, thirty-five years of age, tells us that he has had four attacks of diarrhea in the last year and a half. These attacks last from four to six weeks. They do not seem to be initiated by any unusual dietary indiscretion. When they start he will pass from two to four stools daily, which gradually become less and less formed, though consisting largely of food remnants, and then begin to be largely mucus. The mucus is dark brown in color, comes out in chunks, not in ribbons, and sinks to the bottom of the water in the toilet. There is never any blood. The number of stools gets to be from ten to twenty a day. Each defecation is ushered in by cramps of a rather severe character, accompanied often by slight nausea. He has never vomited.

There is another bit of history which we discovered only after the sigmoidoscopic examination, and which I will recount after I have given you a résumé of the physical findings as they were at the time I first saw him during his second attack.

Physical examination. As you see, he is in good weight. He is rather heavy for his height (5 feet, 11 inches, 198 pounds). He is not at all the enteroptotic type which is usual for cases of mucous colitis, nor has there been any loss in weight due to the diarrhea. Even during attacks he hardly loses more than 5 or 10 pounds, and he quickly gains that back.

The general physical examination is negative.

The nose, throat, and teeth show no foci of infection. The heart, lungs, blood-pressure, thyroid, urine, and blood are normal.

His gastric acidity, read after a single evacuation of gastric contents, was 52 for total acidity. This is certainly not enough to account for his symptoms. There was no demonstrable hypersecretion.

The stools were carefully examined for protozoa many times, always with negative results. He has never lived for any length of time in a tropical country. This, of course, is not necessary to cause infection with amebæ, as many cases have been found in patients who have lived in the northern part of the United States. In this patient, however, many stool examinations

failed to demonstrate any amebæ or even trichomonas which are so frequently found in diarrheal stools (without being necessarily pathogenic) The stools were usually alkaline in reaction. Cultures were plated, and showed colon bacilli always predominating, though some colonies of staphylococci and streptococci were found



Fig. 192—Radiograph of barium enema, Case III. Radiograph was made when the patient experienced no pain. Compare with Fig. 193

The x-ray examination of the rectum and sigmoid was made after the patient had taken a barium enema. It was made during one of his acute attacks when he was frequently experiencing severe lower abdominal cramps. The patient was observed while lying on a troposcopic table and was asked to tell us when he had one of these attacks of pain. Radiographs were taken both during one of these cramps and in intervals

It is interesting to note from the radiographs here reproduced (Figs 192, 193) and taken at both of such periods that the cramping is due to spasm of the descending colon and sigmoid juncture and to spasm of the sigmoid on its right-sided loop

In the interval between these spasms it was noted, and I hope you can see on the radiograph, quite definite small diverticula of the sigmoid

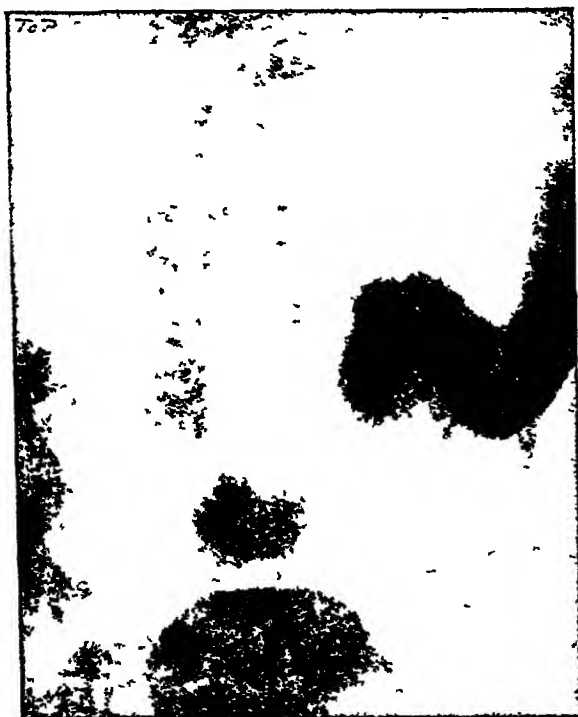


Fig 193 —Radiograph of barium enema, Case III Radiograph was made during severe spasm Note that the sigmoid alone takes part in the spasm

A sigmoidoscopic examination after the barium enema had been evacuated showed a number of small superficial ulcerations in the sigmoid and rectal mucosa These may have been the openings of small sigmoid diverticula They may be spots of localized infection of the muscoa

Summing up the situation to this point we may say that he

had a mucous diarrhea. It was not a typical mucous colitis which produces casts of the bowel, made up of solid white mucus. In this patient there were mucous stools which represented a deep-seated infection of the intestinal mucosa involving the mucous glands of the colon and stimulating them to exaggerated activity. This was not due to a parasitic infection of the colon. It was not due to an ulcerative colitis of the type which involves the entire colon. It seemed to be due to an infection of the lower part of the bowel, of the sigmoid practically alone. What could cause this?

There is no doubt that, partly, it was due to a diverticulosis of the sigmoid. But diverticulosis of the sigmoid alone would not cause it. Was there no other lesion present? In answer to that our sigmoidoscopic examination shows us an infection also present in ulcerative patches possibly about the mouths of these diverticula. In other words, a diverticulitis is also present. What was the cause of this diverticulitis?

To explain this we must submit to you the bit of history which we stated above we were going to withhold until later. We have frequently found it advisable to ask intestinal patients whether there has ever been any rectal trouble. When we had reached this stage of our inquiry with the present patient we asked about this, and the patient told us that he had been bothered a good deal with anal pruritus, and for some time before the diarrhea started he was accustomed to take an enema after every bowel movement, as the accumulation of fecal matter in the rectum, no matter how little, would set up an irritation which caused intolerable itching. He found that if his lower bowel was completely emptied with a small enema the pruritus would be relieved. For this reason he took a small soap-suds enema once a day at least, and often two or three times, if the itching was bad, for a year or more. He always used the same enema tip and never boiled it.

In the light of this story it seems probable to me that he repeatedly infected his sigmoid mucosa with a pus organism from the dirty enema tip which, as is often the case, caused slight superficial ulcerations.

The method of treatment in this and other cases of sigmoid diverticulitis is interesting. The patient during his primary attack was first put upon the ordinary remedies for diarrhea—tannic acid compounds. These did little good unless accompanied by opium. Several times he took a tablet of morphin and atropin. These gave, however, only temporary relief. During the first attack he did not experience any permanent improvement until he eliminated all residue-containing foods from his diet and ate only cream soups, mashed potatoes, milk, ice-cream, soft boiled eggs, etc. Upon this routine he showed quite definite improvement, which lasted several months, when a recurrence of the diarrhea occurred.

Early in the second attack the barium enema was given. After this the diarrhea stopped quite suddenly. It did not recur for two months again, when the non-residue diet and another barium enema stopped it in less than a week. Dudley Roberts has called attention to the value of large doses of bismuth subcarbonate in sigmoid diverticulitis. He says that the bismuth fills up the diverticulæ with a non-irritant antiseptic mixture and prevents activity. It is frequently observed that these patients do well for a time after a diagnostic x-ray examination. In this particular patient the bismuth or barium by mouth do not do as much good as the barium enema. The distention which occurs with the introduction of the enema distends the bowel, stretches the muscle of the sigmoid, fills the distended diverticulæ, and by all these things causes an amelioration of the process. The patient has had one attack of diarrhea which lasted over three weeks, during which time he was not able to get a barium enema, but as soon as he did get one the attack ceased. We have advised him to have an enema at intervals or at least at the first symptoms of the starting of an attack in order to keep the diverticulæ uninfected and quiescent.

CASE IV FERMENTATIVE COLITIS

The principal complaint of this man who is forty-two years old, was discomfort in the abdomen low down mostly on the left side. It had been going on for several years. It was nearly

continuous, but had periods of accerbatation, when there was considerable distention and even pain. Relief was obtained by the passage of large amounts of gas and one or two partially formed mushy stools. He is not willing to say he was either constipated nor that he had a diarrhea. The discomfort, however, was definitely connected with his bowel movements.

Physical examination resulted in the accumulation of no data of any importance. He was rather underweight. Sigmoidoscopic examination revealed no abnormalities.

The x-ray showed a large sigmoid with a redundant loop, but not one that could be said to be very abnormal. The lumen was not enlarged.

The stool, upon examination, was unformed and large. No parasites were found. Numerous undigested starch fibers were discovered. When it was placed in a covered jar gas-bubbles formed in large quantities.

This patient showed a remarkable improvement upon a very simple method of treatment. Upon questioning, after the stool examination, he stated that he had figured out for himself that he needed bran and vegetables to keep his intestines moving. Thus he was on a nearly entirely starch diet. We simply reversed this. We took away practically all his bread, potatoes, bran, and such things, and gave him meat, eggs, gelatins, milk, etc. His reaction was immediate and very favorable. His discomfort stopped. The explosive windy stools were replaced by a single formed stool, and his weight has increased 20 pounds in a year.

SUBPHRENIC INFECTION—CASES ILLUSTRATIVE OF THE DIFFERENT FORMS OF THIS CONDITION

- Case I Fibrinoplastic Subphrenic Inflammation.
- Case II Subphrenic Abscess
- Case III Subphrenic Effusion
- Case IV Metastatic Subphrenic Abscess
- Case V Subphrenic Abscess, Rupturing Through the Diaphragm and Causing Lung Abscess
- Case VI Perforated Gastric Ulcer, Subphrenic Abscess, and Pleural Abscess.

WE present here the records of 6 cases of subphrenic infection, which illustrate quite completely nearly all the varied phases of that interesting condition. They include not only cases of abscess formation in the subdiaphragmatic spaces but also a case of fibrinoplastic inflammation, and a case of subphrenic effusion, a lesion which has hitherto not been described.

The origin of the condition is also well illustrated in this series. Any intra-abdominal infection may extend, by following the cleavage lines of the peritoneal folds between loops of intestines, into the spaces between the liver and the diaphragm on the right, and between the fundus of the stomach and the diaphragm on the left. The most frequent cause is suppurative appendicitis. Perforated gastric or duodenal ulcer is the next most frequent cause, cholecystitis is third in frequency.

There are 4 cases of subphrenic infection originating from appendicitis, 1 from gall-bladder infection, and 1 from perforated gastric ulcer, described below.

Infection of the subphrenic spaces by extension alone is not the only mechanism possible, and we describe a case of metastatic infection by way of the portal vein with primary liver abscesses and secondary subdiaphragmatic abscess.

The complications which are so frequent in the disease are well illustrated in Case V, which began as a suppurative appendicitis and terminated as a lung abscess.

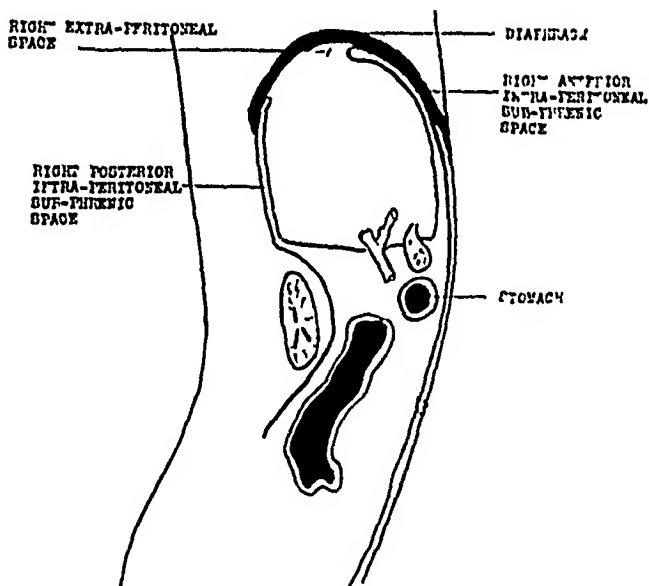


Fig. 194.—Diagram of an ideal vertical section through the body to the right of the midline

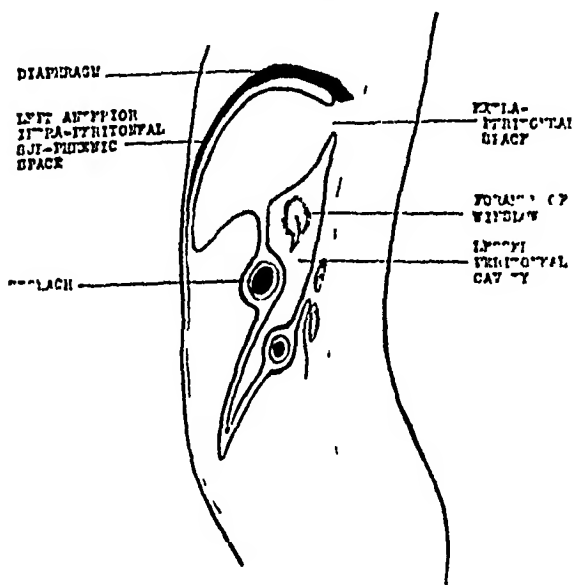


Fig. 195.—Diagram of an ideal vertical section through the body to the left of the midline

The anatomy of the subphrenic spaces should be kept carefully in mind. The student is advised to study the peritoneal reflections of the liver as given in his text-books of anatomy.

Barnard has divided the spaces below the diaphragm into four intraperitoneal and two extraperitoneal areas. This classification is followed by most authors on the subject. The liver

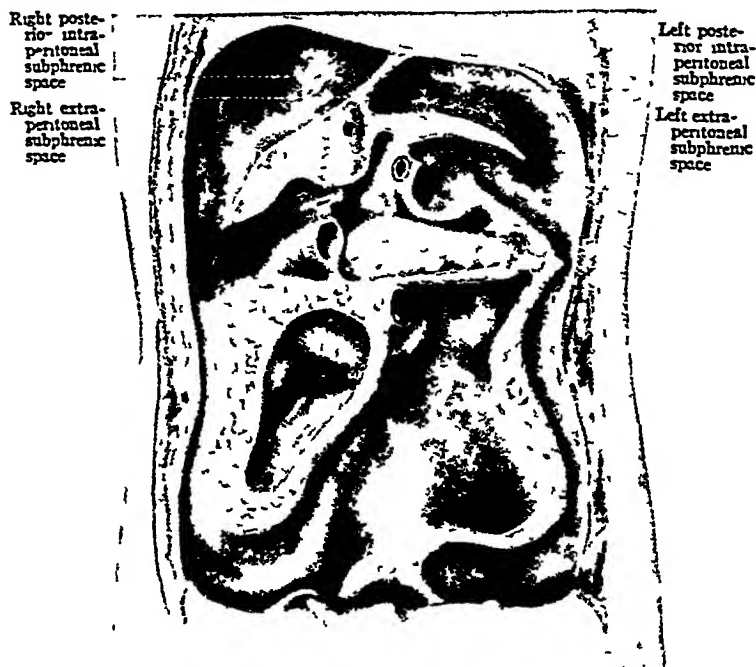


Fig 196—Diagram of the upper abdominal cavity after removal of the liver, stomach and colon showing the subphrenic spaces and reflection of the peritoneum.

is suspended from the diaphragm by the falciform ligament which divides the general space between diaphragm and liver into a right and left part. The peritoneum reflected from the under surface of the diaphragm spreads out from side to side forming two lateral ligaments which subdivide these two primary areas into four, so that we have a right anterior intraperitoneal, a right posterior intraperitoneal, a left anterior, and a left

posterior intraperitoneal space. The peritoneum spreads out leaving uncovered a considerable area on the superior surface of the right lobe of the liver, this space partially separated into two divisions by the top of the small sac of the peritoneum constitutes Barnard's extraperitoneal spaces—right and left.

The signs of abscess formation in one or the other of these spaces will differ with the location of the abscess.

In recounting these cases I shall not bore you with a formal tabulated clinical history and set of physical findings, but I will sketch the symptoms, signs, and progress in the order in which they presented themselves as clinical problems.

CASE I. SUBPHRENIC INFLAMMATION

This young lady was seen in consultation with Dr H P Kuhn at St Luke's Hospital, on December 22, 1920, eleven

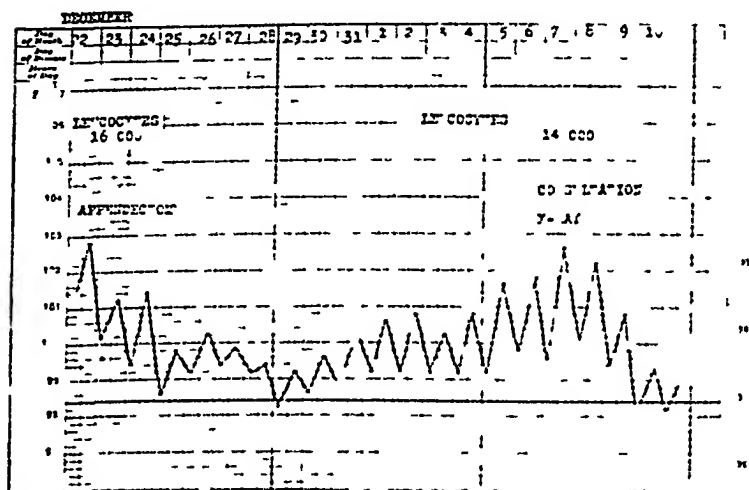


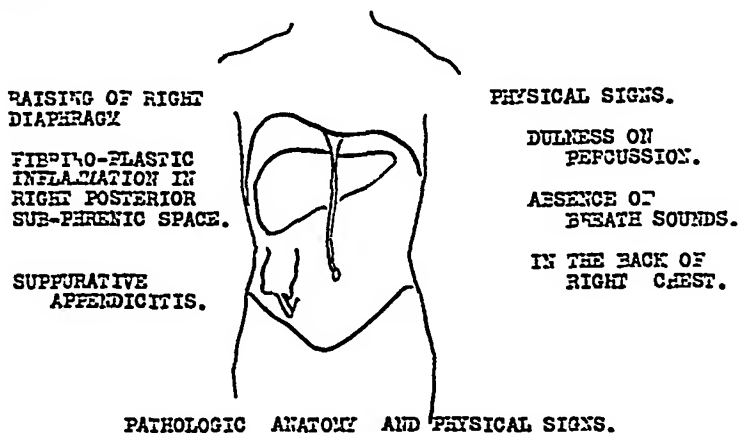
Fig 197—Chart of Case I

days after an appendectomy. At this time her temperature had taken a sudden exacerbation. She also complained of pain along the right costal border. The course of the temperature from the time of admission through the course of her illness is shown in Chart I.

Physical examination showed some tenderness and rigidity over the right upper abdominal quadrant

The most marked signs, however, were in the back of the right chest, where there was made out an area of dulness extending well above the angle of the scapula. Breath sounds over this area were absent or very feeble. There was no marked strip of hyperresonance above the upper border of the dulness.

The leukocytes at this time were 10,000 per cubic centimeter.



CASE I.

Fig 198

A radiograph was obtained, herewith reproduced (Fig 199). It showed a high right diaphragm and a rather indefinite rounded shadow above it. The lungs appeared clear.

The diagnosis rested between pleural effusion and subphrenic abscess. The x-ray picture was not characteristic of fluid in the pleural cavity, which in the great majority of instances accumulates first in the outer corner of the chest, in the very outmost supradiaphragmatic angle.

This question of the prominent thoracic signs arises constantly in subphrenic inflammation, and I wish to call your attention to it very emphatically. When pus accumulates in the right posterior intraperitoneal space, which frequently occurs by

direct extension from the appendix, the route of which may be seen quite readily by consulting an anatomic vertical section through the trunk of the right side, it pushes the diaphragm upward and flattens it out against the posterior chest wall. There is also a fixation of the diaphragm which probably causes a partial atelectasis of the inferior right pulmonary lobe, with consequent signs of dulness and absence of breath sounds.



Fig. 199 — Radiograph of chest of Case I

In this case the previous appendix history pointed so strongly toward subphrenic infection as against pleural effusion that it was decided to wait and observe the patient a few days before arriving at a definite diagnosis. This was a fortunate decision, because in a few days the temperature returned to normal, the signs subsided and the patient entered upon a normal and complete convalescence.

A fibrinoplastic subphrenic inflammation not progressing to pus formation has been described by Dr Roger I Lee. This case seemed to be of this character. The patient certainly had both signs—the temperature is one which could not have been influenced by the personal equation of the examiner—and symptoms of trouble in the upper abdomen and lower chest. They could not have been due to pus because the patient has been seen frequently since the time of examination, and has remained in good health. Dr Lee's cases had nearly exactly similar signs and likewise recovered without operation.

CASE II SUBPHRENIC ABSCESS

This patient presents a pure type of subphrenic abscess, one of the least complicated of any in this series. He is a man

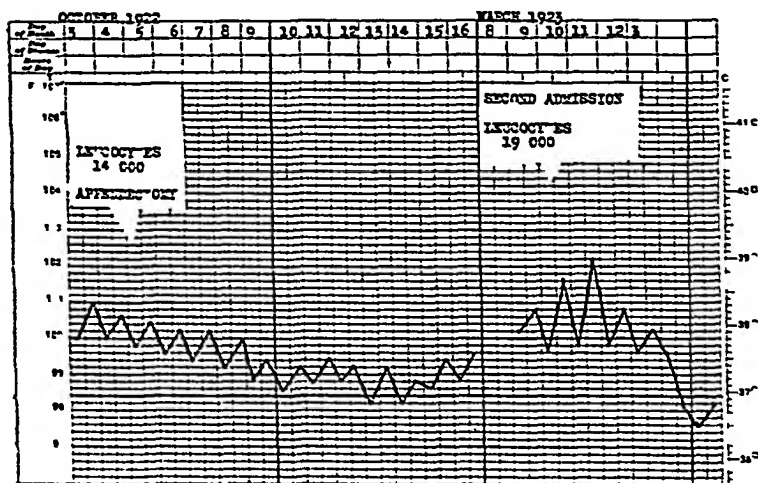
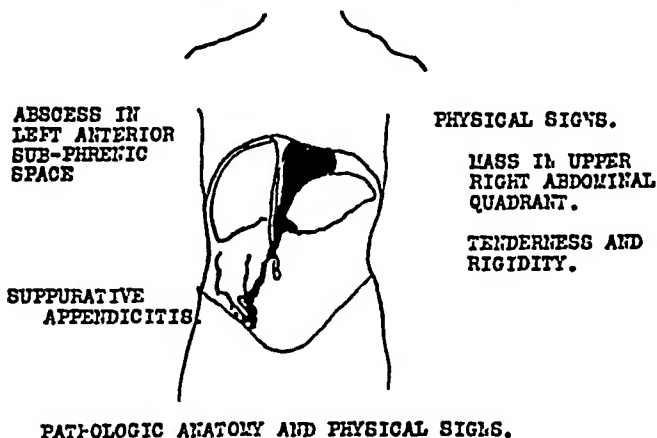


Fig 200—Chart of Case II Interval between first and second admissions to hospital indicated

aged twenty-six, who was operated on by Dr H P Kuhn in St Luke's Hospital October 3, 1922. A suppurative appendix was removed and a drain inserted. At the time of operation his leukocyte count was 14,000. I wish to call your attention to the temperature record of his first stay in the hospital (Fig 200). The

temperature never stayed continuously at normal, and at the time of his discharge was just a little over 99° F. As no physical signs sufficient to account for this rise of temperature could be found, it was ascribed to the general preceding infection and the processes of repair, and he was discharged at the end of two weeks with a closed, well-healed wound. In the light of subsequent events this continued increase of temperature is important and instructive.

He re-entered the hospital on March 8, 1923, nearly five months after discharge. He then had a temperature of over



CASE II

Fig 201

100° F, and a leukocyte count of 19,000. He said that he had not felt well since the operation, that he had had some chills, and that he had had fever every day. He complained of continuous dull pain over the upper right quadrant of the abdomen. On physical examination, a distinct rigidity could be made out over the gall-bladder region and a mass with indistinct edges felt. This mass extended several fingerbreadths below the costal margin. Otherwise the physical examination was entirely negative. It is worth noting that there were no findings in the chest behind. The x-ray showed a clear thorax, the radiograph is reproduced (Fig 202). I submit, subject to your own opinion,

that the right diaphragm is not particularly high. When abscesses form to the left of the falciform ligament little change occurs in the diaphragm on either side.

Incision was made over this mass. The mass was found to be the left lobe of the liver pushed down, and a rolled up omentum adherent to liver and anterior peritoneum. Beneath this a good



Fig 202 —Radiograph of chest of Case II

quantity of pus was evacuated from the left anterior intraperitoneal space. Prompt remission of temperature ensued and eventually complete recovery occurred.

This case is a sharp example of a subphrenic abscess pointing abdominally. This occurs when the left anterior intraperitoneal subphrenic space is involved.

CASE III SUBPHRENIC EFFUSION

The patient, an enormously stout woman forty-seven years of age, was seen in consultation with Dr H S Hickok. Her principal complaint was pain over the upper right quadrant of the abdomen. She had suffered from this for several years and had had a number of acute colics. At the time of examina-



FIG. 20. —Radiograph of chest of Case III

tion she had a temperature of 99.8°F and a leukocyte count of 16,000.

Physical examination was very interesting. The back of the right chest was very dull from below upward to beyond the angle of the scapula. No heart sounds could be heard over it. The radiograph, which was not clear owing to the great thickness of the body, showed a shadow half way up the right chest.

A diagnosis of pleural effusion was made. This was wrong and the mistake is worth noting.

A diagnostic puncture of the chest was made, but no fluid obtained. So strongly did I feel that an effusion was present that I obtained permission to anesthetize the patient and made several attempts to localize the fluid. I put the needle in the posterior chest wall several times, with negative results. Finally, low down in the axillary space I obtained a syringe of clear fluid, which contained lymphocytes under the microscope.

Under these circumstances my own diagnosis was still pleural effusion. However, Dr Hickok, the surgeon in charge of the case, was not convinced. He was certain there was a gall-bladder infection and he made a laparotomy incision over the gall-bladder. This proved a very fortunate move because a gall-bladder full of pus and stones was found, with a closely adherent omentum, and a large amount of serous fluid beneath the dome of the liver and located in the omental folds. The gall-bladder had not ruptured.

In this case the marked signs of dulness in the right back presented a diagnostic problem which was incorrectly solved. The finding of clear fluid simply confirmed me in my mistake. I find no reports of serous effusion in the subphrenic space in the literature.

CASE IV PYLEPHLEBITIS OF THE PORTAL VEIN AND SUBPHRENIC ABSCESS

The patient, a young man aged twenty-five, was first seen in my office in consultation with Dr H P Kuhn on March 8 1921. He had come from his home, a small village about a hundred miles away. The history is valuable.

His family—father, mother, and 4 brothers—were living and well. His wife had died at the age of twenty-one of pulmonary tuberculosis.

He had a severe suppurative appendicitis with appendectomy two years before I saw him. He reported that he had constant drainage from the wound for a year following the operation. Then another operation was done, but the drainage continued.

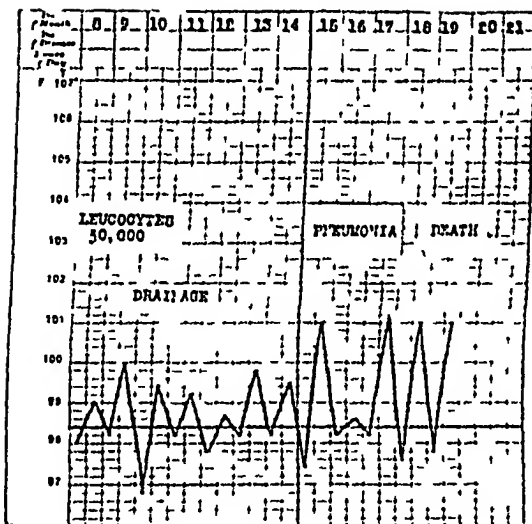
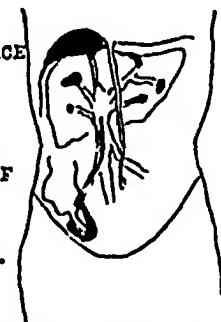


Fig. 204 —Temperature chart of Case IV during stay in hospital

ABSCESS RIGHT
SUB-PHRENIC SPACE

MULTIPLE LIVER
ABSCESES

RESULTING FROM
PYLE-PHLEBITIS OF
PORTAL VEIN
FROM
SUPPURATIVE
APPENDICITIS.



PHYSICAL SIGNS.

ENLARGED LIVER.

ASCITES.

PALLOR.

SEPSIS.

PATHOLOGIC ANATOMY AND PHYSICAL SIGNS.

CASE IV.

Pl. 205

The drainage at times had a fecal odor. It usually was pus, but sometimes was bloody. He complains of little pain except occasionally gas rumbling and colic in the abdomen. He has



Fig. 206 —Photograph of patient (Case IV) Note enlarged abdomen, scarring on skin of abdomen, and emaciation

lost 20 pounds in weight, and has done no work any time since the original operation

On physical examination the first thought was that he was

a very sick looking boy. He had a pallor and the general look of sepsis.

When he was stripped the appearance of the abdomen immediately drew attention to it. So remarkable was it that we had a photograph taken which is here reproduced (Fig 206). The abdomen was greatly enlarged, as in an ascites. This is



Fig. 207—Radiograph of chest of Case IV

only faintly shown in the photograph. There was evidence of fluid in the abdomen. The liver could be felt almost at the umbilicus. But by far the most striking thing was the occurrence of numerous scars on the skin surface of the abdomen. They had the appearance of fistulae, and while some were covered over, from others could be squeezed a thin serous fluid. There was an open fistulous appendectomy wound.

The temperature was 99.6° F

The leukocyte count was 30 000, 88 per cent were polymorphonuclear neutrophils

The fingers were clubbed

The rest of the physical examination was negative. The heart and lungs presented no abnormal signs. The urine was negative. The Wassermann reaction was negative.

The x-ray study of a barium meal showed a low hepatic flexure due to the enlargement of the liver.

The radiograph of the chest (Fig 207) is herewith reproduced. It showed a high right diaphragm, and a thoracic cavity clear save for some curious mottled shadows which have never been explained.

A diagnosis of subphrenic abscess was made.

A laparotomy was done and over a pint of thick pus drained from the right anterior and posterior intraperitoneal subphrenic space. The liver was found enormously enlarged. No other findings were noted at operation except the extensive adhesions.

The patient died two weeks after operation of lobar pneumonia.

At autopsy the liver was found to be riddled with small abscesses. The abscess cavities were filled with a cheesy thick pus from which staphylococci were cultured. Under the microscope they were seen to be almost always in relation to a portal venule. The portal vein was filled with a dark sandy thrombus. The right lung was the seat of a hemorrhagic pneumonitis. The fistulae on the skin surface of the abdomen were superficial.

This is an example of metastatic subphrenic abscess. The appendicitis had initiated a septic portal pyelphlebitis which deposited septic material in the substance of the liver. One of the abscesses under the capsule of the dome of the liver probably ruptured, infecting the subphrenic space.

CASE V RUPTURED SUBPHRENIC ABSCESS

(This case is reported through the courtesy of Dr P. T. Bohan and Dr A. E. Hertzler on whose services at the Bell Memorial Hospital of the University of Kansas, it occurred.)

The history of this patient is very long and complex, only a summary is proper in this place

A male, aged forty-two, entered Bell Memorial Hospital September 13, 1922 His disability dated from 1915, when he had an appendicitis The appendix was not removed until July, 1919 No drainage was put in at the original operation, but nine days later the wound was opened and a quantity of pus evacuated The wound drained for two months The patient did not leave the hospital until October He was told

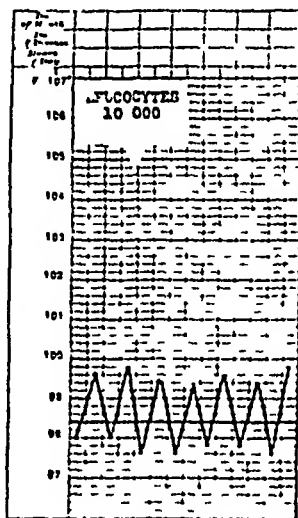


Fig 208 —Chart of Case V

he had contracted typhoid fever in the hospital When he went home he was coughing and expectorating quantities of thick foul pus In June, 1920 he was sent to New Mexico, with a diagnosis of pulmonary tuberculosis While in a sanitarium there attempts were made to find fluid in the chest He has consulted various clinics and diagnosticians, but no correct or definite diagnosis has been made

At present he complains most of the cough and expectoration Every two or three weeks the right side of the chest

will get to feeling full, and finally he will cough up a great load of pus for a few days, and then things will subside

Physical Examination—The temperature record for a few days in the hospital is reproduced

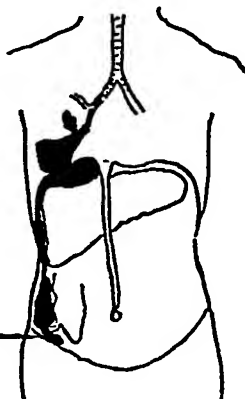
The right thorax is markedly contracted and does not move with respiration

The right chest has marked dullness in the axilla. There are crepitant râles in the right axilla. The breath sounds over the right chest are distant. The expiration is prolonged, the whispered voice feebly transmitted.

LUNG ABSCESS
FORMED FROM
RUPTURE OF SUB-
PHRENIC ABSCESS
THROUGH
DIAPHRAGM.

EXTENSION OF
INFECTION ALONG
PERITONEAL FOLDS.

SUPPURATIVE
APPENDICITIS,
PROBABLY RETRO-
CAECAL.



PHYSICAL SIGNS:
EXPECTORATION OF
FOUL SPUTUM FROM
RUPTURE OF ABSCESS
INTO MAIN BRONCHUS

DULLNESS AND RÂLES
IN RIGHT AXILLARY
SPACE,

PATHOLOGIC ANATOMY AND PHYSICAL SIGNS.

CASE V.

Fig 209

Blood—Red cells, 5,329,000 Hemoglobin 90 White cells 10,800, 74 per cent polymorphonuclear neutrophils

Urine—No abnormal findings

Sputum—No tubercle bacilli

Radiograph of chest (Fig 210) The right chest is the site of extensive retraction of the chest wall and infiltration of the lung

Operation, local anesthesia, April 4, 1922, by Dr A E Hertzler Incision made in axillary line The pleura was thick

and adherent. A needle reached pus in the subphrenic space, and drainage was instituted.

Subphrenic abscess frequently ruptures through the diaphragm and through the pleura, causing empyema of the pleural cavity and lung abscess. I have records of 2 other cases, one seen at autopsy, in which an appendiceal abscess burrowed its



Fig. 210.—Radio, raph of chest of Case V. Note retraction of ribs on right side, and evidences of extensive intrathoracic inflammation.

way under the diaphragm, then through the diaphragm through lung tissue, finally rupturing into a bronchus.

It is instructive that the diagnosis in this case was so frequently missed by competent men. This serves to emphasize the fact that subphrenic abscess and its complications deserves more consideration from the profession.

CASE VI. RUPTURED GASTRIC ULCER

This is a remarkable and instructive case

I first saw this patient in 1911. She was the victim of a marital syphilitic infection, and had a neglected gumma of the left tibia, which had broken through the skin and was discharging necrotic material. On large doses of iodids and mercury she showed only slight improvement, and as she insisted on getting about, a pathologic fracture resulted and the leg had to be amputated. After this I lost sight of her until ten years later, October, 1921, I was called to see her again, and found her complaining of shortness of breath and swelling of the abdomen. The pulse was rapid, though regular, there was evidence of ascites, and of fluid in the back of the left chest. With the old history of syphilis in mind the diagnosis was either myocardial failure or luetic hepatitis, and she was placed in a hospital, upon digitalis, the iodids, and tapping.

Paracentesis abdominis resulted in the withdrawal of some serous fluid with fibrinous flakes rather conspicuous in it. The three tapplings which were made did not, however, reduce the size of the abdomen to any appreciable extent. The last tapping was nearly a complete failure. Thoracentesis also removed a considerable quantity of serous fluid.

The patient became dissatisfied with progress, left the hospital, and employed another medical attendant. Quite by accident I learned the final outcome of the case.

About two months after I saw her last she entered the City Hospital. My colleague on service there, Dr. Harry Jones, having obtained the history of my attendance, kindly gave me the later history of the case. The patient died in the City Hospital December, 1921, and at autopsy a perforated gastric ulcer was found with abscess in the lesser peritoneal cavity rupturing through the diaphragm and causing empyema of the left pleural cavity. No history of ulcer or of the perforation had ever been obtained during life.

DISCUSSION

Subphrenic infection should be suspected whenever a suppurative appendicitis is followed by an unsatisfactory period of convalescence, with evidences—fever and leukocytosis—of infection not otherwise explained. Its occurrence is not infrequent, and diagnosis is missed with great regularity. Early and accurate diagnosis is all the more important in that serious complications may ensue. The abscess may rupture through the diaphragm into the thorax and cause empyema and lung abscess.

The symptoms are usually vague—weakness, fatigue, loss of weight, fever, rarely chills, and unlocalized upper abdominal pain are about all in the uncomplicated cases.

The signs may be of two general sorts, abdominal and thoracic, depending upon the anatomic location of the abscess. On the right side, which is the usual site, the abscess will point either abdominally in front at the right upper inner abdominal quadrant, or in the right lower thorax behind.

The abdominal signs are those of any intra-abdominal infection—rigidity, tenderness, leukocytosis, etc. The thoracic signs are due to the accumulation of an abscess in the posterior and anterior right intraperitoneal subphrenic space, pushing the diaphragm up, which can occur to an astonishing height, flattening the diaphragm out against the posterior thoracic wall, causing dulness and the absence of breath sounds.

Pleural effusion is the condition which must be differentiated most frequently from subphrenic abscess. Lockwood states, in a differential table, that the two diseases can be distinguished because pleurisy with effusion is more common following influenza or pneumonia, that it causes rapid respiration, that the temperature is not of the church steeple type, that the level of dulness changes on change of position of the patient, that the heart is frequently displaced, and that dyspnea and cyanosis are common. I regret that in my experience the matter is not so simple. Pleural effusion, of the type causing diagnostic doubt, is not a sequel of influenza or pneumonia, it seldom or never changes the respiration usually being tuberculous, in

origin, it does cause a low morning and high evening temperature, the level of dulness never changes in uncomplicated (*i e*, non-pneumothorax) cases of pleural effusion on change of position of the patient, the heart is seldom displaced, dyspnea is rare, and cyanosis almost unknown. The very points which make the diagnosis so puzzling are that, in both diseases there occurs dulness with absence of breath sounds over the back of the chest, without previous history of thoracic disease, with a septic type of fever, with no change of position of the level of dulness on change of position of the patient. In differential diagnosis the history is important, the connection of events from the original appendicitis or other intra-abdominal infection is usually clear. The radiograph shows a sharper level of the diaphragm than will occur in any type of pleural effusion. Perhaps the most valuable differential diagnostic method of all is the exploratory needling of the chest.

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CLINIC OF DR HARRY C BERGER

CHILDREN'S MERCY HOSPITAL

A CASE OF PURPURA HÆMORRHAGICA—TRANSMISSION OF HORSE SENSITIZATION OF DONOR BY WHOLE BLOOD INJECTION—RAPIDITY OF ABSORPTION

THE use of normal saline and glucose solution hypodermically, intramuscularly, intraperitoneally, and directly into the blood-stream has become a well recognized and familiar therapeutic measure, for various conditions arising in pediatric practice, such as the dehydration in prolonged vomiting, acidosis, marasmus, septicemia, etc, as well as in surgical shock and indications of this type

This I am more and more frequently supplementing with intramuscular injections of whole blood in marasmic and septic infants, though I do not yet subscribe to the practice of using whole blood intraperitoneally for this purpose. Blood used in this way has not been submitted to tests for type, the saving of this time and inconvenience being considered one of the advantages of giving blood intramuscularly rather than intravenously

If the donor is of the patient's immediate family, or if he is clinically free from infection and has a negative Wassermann reaction, he is considered satisfactory

Many such injections of whole human blood have been done with no complications or objectionable results having arisen

The case I want to present now, however, shows that even this simple procedure may be attended by results which are highly objectionable, especially if they should persist and become permanent

It also shows the rapidity with which fluids begin to be absorbed when given intramuscularly

Artificial protein sensitization in the human, such as we commonly produce in our laboratory animals, is still a matter for some discussion. Whether a sensitization in one individual can be directly transmitted to another by blood transfusion I believe has been held as a moot question. An interesting case of this type was reported by M. A. Ramirez, in 1919.¹ In the case I wish to present it would seem that at least a temporary sensitization to horse-serum was effected by this procedure.

My own family history, so far as I am able to determine on careful inquiry, yields no history of asthma, eczema, or other evident allergic manifestation. During my "teens" I was frequently about horses without at any time experiencing the slightest disturbance. In more recent years, however, I find that horse-serum gives me a severe reaction, and the dander from the horse precipitates an attack of asthma.

Case I—Johnnie W. aged eighteen months was brought to the Children's Mercy Hospital on May 6th from a small town in Nebraska accompanied only by a friend of the family, with the following meager history:

Family History—Father, mother, and 3 older children living and well. No deaths. No miscarriages. No known tuberculosis or other disease in the family.

Personal History—Unknown.

Past History—Has had no severe illness and no contagion, except smallpox some time ago, exact date unknown.

Present Illness—About a week before entrance to the hospital the hands and feet began to swell, and sugar was said to be present in the urine.

Physical Examination—Temperature, 101° F., pulse, 120, respiration, 35, weight, 19 pounds, 6½ ounces, fairly well developed, poorly nourished, somewhat rachitic, white, male child, pasty complexion, eyes normal, ears normal, tongue coated, tonsils large, cryptic, red, but free from exudate, no adenopathy, heart normal in size and position, no murmurs heard, lungs

¹ Ramirez M. A. Horse Asthma Following Blood Transfusion. Case Report Jour. Amer. Med. Assoc., 73, 984, September 27, 1919.

normal, abdomen, no tenderness, no muscle spasm nor masses palpated, liver and spleen not palpable, extremities, no deformity, reflexes normal, right hand swollen, left hand and forearm swollen, painful, and slightly bluish discoloration in spots, right foot, blue discoloration median side of foot, some edema, left foot, more edema than right, but no discoloration of skin

Inside of left auricle upper half is purplish red, no swelling, otherwise, skin is negative except for general pasty appearance White blood-cell count, 19,000 Hemoglobin, 80 per cent Differential cell count Polymorphonuclear, 68 per cent, large mononuclear, 12 per cent, small mononuclear, 20 per cent. Urine—amber clear acid, specific gravity 1010, albumin negative, sugar negative, no pus or red blood-cells present Negative for occult blood Nose and throat, culture negative for diphtheria x-Ray report "Evidence of rachitic changes involving long bones, manifested by flaring of shaft at epiphyseal line and definite thickening at this point No other changes to note"

May 7th Stools very dark brown Temperature 102° F No change in general condition Stools show a positive guaiac reaction Horse-serum, 20 c c, given intramuscularly Throat treated with silver nitrate, 10 per cent.

May 8th Stools blood stained Hemorrhagic area right auricle larger Large hemorrhagic area over right knee cap Swelling of hands and feet less marked Temperature 102° F

May 9th Stools bloody (considerable bright red blood) Hemorrhagic area in right auricle extending Whole of tip of nose hemorrhagic Also many ecchymotic spots on dorsal surface of right hand Swelling of extremities has not increased Heart normal, 20 c c horse-serum given Temperature 99° F

May 10th No fresh hemorrhagic areas Child seems stronger Stools show less blood Temperature 98° F, 20 c.c horse-serum given intramuscularly Urine—straw color, alkaline, specific gravity 1030, albumin negative, sugar negative, no pus or red blood-cells in sediment

May 11th Stools good Temperature 99° F Appetite better General condition improving, 10 c c antistreptococcic serum given

May 12th During the night a hemorrhagic area 5 inches in diameter developed about the umbilicus. A few small red spots bordering this area appear as though they might have been small wheals. Large hemorrhagic area on right knee. No serum given.

May 13th Hands and feet badly swollen again. Palms of hands show a dark blue discoloration. Area over right knee and abdomen larger and a new hemorrhagic area has developed over the left knee. Heart normal. Does not take feedings at all well. 6 30 P M Hemorrhagic area over abdomen is much larger this evening and seems deeper, 20 c c antistreptococcic serum was given intramuscularly.

May 14th I asked Dr. Dwyer to see this child and he agreed with the diagnosis of purpura hæmorrhagica, and also that whole blood seemed essential since the normal horse-serum and antistreptococcus serum had failed to arrest hemorrhage, there having been 80 c c of normal horse-serum and 30 c c of antistreptococcic serum given. The child's friend had returned home and there was no available donor, so I volunteered to give a small quantity of blood. Having been Wassermann tested it seemed this would be wholly acceptable.

At 1 P M 35 c c of my blood was taken up in a syringe and injection into the muscles of the child's thigh was started. Considerable force was exerted on the plunger to empty the syringe as quickly as possible. In a few seconds, when approximately one-third of the blood had been injected, a most extreme urticarial reaction took place. By the time the whole amount of blood had been given huge wheals covered the entire body surface. Nowhere on the face, neck, trunk, or extremities was there a square inch of body surface free from this reaction, which in some parts showed a tremendous elevation above the general skin level. The mucous membranes of the mouth and eyes were free from swelling. There was slight dyspnea, and a hypodermic dose of adrenalin was prepared, but it was not required for respiratory difficulty.

6 30 P M Only small scattered wheals remain, particularly over trunk. Less swelling of hands and feet than yesterday.

Deep hemorrhagic areas right hand, right foot, both knees, and abdomen remain, and many fine ecchymotic spots are scattered over the abdomen and chest Antistreptococcic serum, 28 c c., was given intramuscularly with moderate increase in urticarial reaction

May 15th Stools are good, showing, however, a trace of blood at times Takes feedings well Temperature normal No fresh hemorrhagic areas

May 16th General condition improving Small amount of edema of scalp No further hemorrhage

May 18th No edema of scalp Hands and feet practically no swelling No further hemorrhage Appetite good Wants to sit up in bed Seems much better

May 19th. "High caloric diet" and cod-liver oil started

May 21st Small ecchymotic spots appeared on both feet, 20 c c horse-serum given A severe urticaria resulted, however, this is not nearly so severe as on May 14th when blood was given

May 22d No change Horse-serum, 20 c c, was given with aggravation of urticaria, which is quite severe

May 23d Few hemorrhagic spots appeared on left leg

May 24th. Starting to play and smile, 20 c c horse-serum given, with urticaria resulting

May 28th No hemorrhagic areas to be found Child seems normal in every way except for malnutrition This child has now apparently entirely recovered

The explosive reaction in this child instantly upon receiving a small quantity of my blood, following the repeated injections of horse-serum, a part of which was apparently stored in his tissues, would seem to show that a part of my sensitization to horse-serum was immediately transferred to him in my blood, for the time being at least The rapidity of the absorption and reaction seemed quite remarkable A portion of my blood must have been absorbed immediately to produce this reaction. Considering the large caliber of the needle it is most unlikely that any of my blood could unintentionally have been injected into a blood-vessel It seems to me to show very nicely the

rapidity with which absorption can take place from injections into muscular tissue

The next injection of horse-serum, eight days after the blood was taken, with rather severe urticaria, shows that the sensitization still remained, but probably in a lesser degree. Subsequent injections also produced an urticaria.

Whether this condition will remain permanently is problematic.

I have on three other occasions been the donor of small amounts of blood to children. In none of these cases had horse-serum been given previously or subsequently to the blood injection, and no reaction occurred.

A CASE OF HIRSCHSPRUNG'S DISEASE UNUSUAL METHOD OF MANAGEMENT

THE next case I want to present has been of considerable interest to me, because of the response we have had to an unusual method of management

This boy, born August 22, 1918, first presented himself in the Out-patient Department of this hospital November 19, 1920 with the following story

Complaint—Bowel trouble

Family History—Mother is not strong Father living and well One sister living and well No deaths No miscarriages No history of any tuberculosis or other disease in the family

Past History—Born at full term—normal delivery—birth weight unknown—breast fed till on general diet Has had no contagion except influenza

Past Illness—When the baby was born the mother noticed a “puffing out” just below the ribs, more marked on the left side, and remarked about this to her doctor The child is very constipated The bowels sometimes have not moved for a period of seven days This is not relieved by castor oil or enemata Diarrhea alternates with this severe constipation At times vomits and complains of pain in the stomach

At this time the Out-patient physician who saw him recorded “Enlarged pendulous abdomen Question of Hirschsprung’s disease Desire x-ray examination of intestinal tract.”

He did not return again until May 2, 1923, and I find no social service note for this period

At this time he weighed 39 pounds, temperature 99.4° F. There has been no improvement except for a short time, when receiving massages Diet has been mainly of milk, eggs, and bread Distention is more marked in the evening There is considerable gas, bowels move only with enemata Stools are then foamy, dark green, and of a foul odor At this time physical findings were essentially as on admission to the hospital Therapeutic measures were advised, but not followed out

August 29, 1923 the child was again brought to the Out-



Fig. 211 Taken during the second week after treatment was started. Showing the large protruding abdomen.

Fig. 212—October 22d showing the reduction in the abdomen since treatment began—less than eight weeks.

patient Department, and the mother was persuaded to have the child admitted to the hospital.

When I saw him I found a fairly well-nourished and developed white male child. Weight $39\frac{3}{4}$ pounds. Temperature normal. Color rather sallow, mucous membranes good color. Eyes, ears, mouth, and throat normal. No superficial adenopathy. Muscle tone fair. Heart and lungs normal. The abdomen was enormously distended, to such a degree that satis-



Fig. 213 —Plate showing x ray of sigmoid after barium meal—August 29th

factory palpation was impossible (Figs 211-212). The attempt at palpation set up a marked peristalsis and the intestine stood out through a moderately thick abdominal wall dividing the abdomen into two parts. The furrow thus formed was considerably over an inch in depth and extended in a line drawn from the right nipple to the left anterior superior spine of the ilium. This maintained its position for a considerable time and could for many days

afterward be produced at will At times a hard, very irregular mass about the size of my thumb could be felt at the upper end of this depression The surgeons agreed with me that this was probably a mass of fecal matter

Rectal examination disclosed, with the finger inserted slightly more than 2 inches, a structure shelving out into the rectum, which felt like scar tissue under tension However, it did not seem extensive enough to produce any degree of obstruction, otherwise rectal examination was negative

Genitalia normal

Extremities normal

Reflexes normal

Nothing remarkable in laboratory findings

x-Ray after barium meal showed the upper intestinal tract to be normal

Figure 213 following a barium enema shows nicely the position and extent of the sigmoid It also explains the production of the transverse furrow mentioned in the physical findings

Figure 214 was made five days after Fig 213 No additional barium having been given, this being the retention over this period of the previous enema

What are the outstanding points in this case?

In the history

First This child has always been very constipated, going at times as long as a week without a bowel movement

Second Large doses of castor oil failed to produce a stool, sometimes even an enema failed to do so

Third Intermittently there was a diarrhea for a time

Fourth There was considerable gas and the stools were foul, dark green, and foamy

Fifth Vomiting and abdominal pain at times

Sixth The mother noted a bulging out of the abdomen more marked on the left side in early infancy

Physical findings

First A fairly well-developed and rather well-nourished child

Second The extremely large protruding abdomen

Third The tremendous peristaltic action with the formation of the groove before mentioned

Fourth The intrarectal structure felt on digital examination.

Fifth The large, redundant sigmoid seen in the x-ray plate following barium enema



Fig 214—Plate showing x ray made September 3d no further barium having been given This shows the retention present following barium enema given August 29th

This condition may be congenital (Hirschsprung's disease) or acquired If acquired it may be due to a continual abuse of the intestinal structure from chronic indigestion, particularly of the carbohydrates, or a weakening of the musculature of the

intestinal wall as a part of a general muscular weakness found in such conditions as rickets, or due to a partial obstruction of the lower bowel (Such a case I saw some time ago, where the stricture would not admit a French No 16 catheter, and on operation a small pan of plum pits, buttons, pennies, wire



Fig 215—Plate taken immediately after barium enema October 22d, showing the reduction in the lumen of the sigmoid. Note that barium fills the transverse colon.

staples, etc., was recovered.) The fact that the symptoms in this child were noted by the mother since early infancy, and that she also noted what she describes as a "puffing out of the abdomen, more marked on the left side" since this early time, and the fact that he is quite well nourished, with the fact that he has no lower bowel obstruction places him definitely in the

class of a congenital dilatation of the colon or Hirschsprung's disease

What are we doing for this child?

Upon consultation with the surgeons it was agreed that medical treatment should be given a trial. A large saline cathartic was given, with no result. Repeated high irrigations with a rectal tube gave better results. The orthopedists were consulted and an elastic binder was made by a local supply house. This gave so little support and caused so much local irritation that it was abandoned after the third day of its use. Owing to the absence of our regular masseuse, massage has been used rather indifferently.

He was started on a soft general diet with carbohydrates restricted as much as was practical.

On August 31st he was started on pituitrin (bulk package) 10 drops by mouth four times daily. This was increased to 12 drops four times a day on September 7th.

Rectal dilatation every alternate day was also started August 31st. We are not dilating so frequently now but are dilating 3 fingerbreadths, with no incontinence of feces. There is still considerable tendency toward constipation which requires enemata at intervals.

I consider him still very far from well, but you will not find it difficult to judge the improvement by comparing his present appearance with the picture made in the second week of his treatment, or by comparing the x-ray of his barium enema made today (Fig 215) with these plates made on admission.

The progress made I attribute to

- 1 Rectal dilatation
- 2 Diet
- 3 Pituitrin
- 4 Enemata

CLINIC OF DR. FRANK C. NEFF

CHRISTIAN CHURCH HOSPITAL

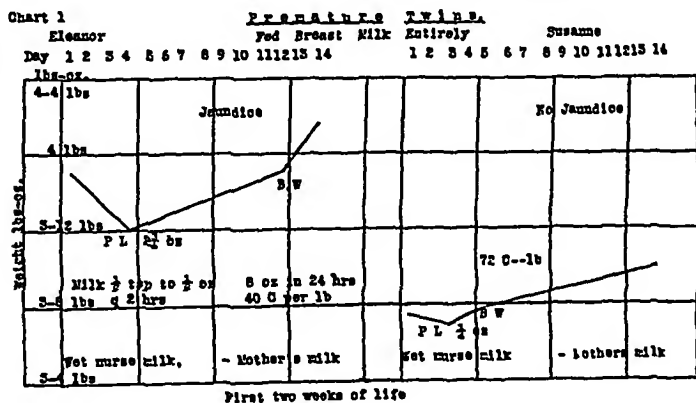
THE CARE OF PREMATURE TWINS AND TRIPLETS

THE speaker wishes to present this morning the weight charts of two sets of twins and one of triplets, the former under hospital observation for a portion of the time and later in the home, the latter entirely in the home. These infants represent the hopeful cases of prematurity, as they were all above 3 pounds at birth, and with one exception were soon vigorous enough to nurse, swallow, or retain all of their food in whatever manner it was given. With the application of external heat there was no difficulty in keeping their body temperature at a uniformly normal degree.

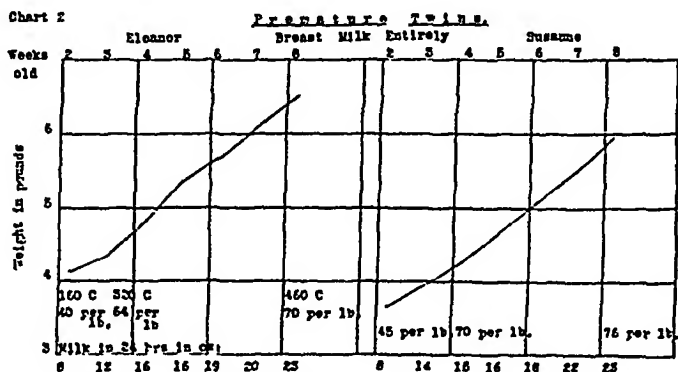
These twins, Eleanor and Susanne, were born six weeks before their expected time. Eleanor weighed 3 pounds, 15 ounces, had a physiologic loss of $2\frac{3}{4}$ ounces at the fourth day, regained her birth weight at the twelfth day, and weighed 4 pounds, $1\frac{1}{2}$ ounces on the fourteenth day. She was able to nurse her mother on the third day, before and after which time she was fed, with a dropper, tube, or Breck feeder, diluted or whole milk from wet nurses in measured amounts suitable to her needs and tolerance. As the wet nurses had not had Wassermann tests all milk from such donors was boiled for five minutes without any evidence of injurious effect upon the infant. Such boiled milk was used for several months.

Susanne weighed 3 pounds, $7\frac{1}{2}$ ounces, was not so vigorous, cried feebly, had difficulty in swallowing, and was fed with a Breck feeder attached to a catheter. Her physiologic loss was so little as to be measured with difficulty $\frac{1}{4}$ ounce at the third day, regaining her birth weight on the fifth day, weighing 3

pounds, 10 ounces on the fourteenth day. She was unable to nurse at one week following, which time she was fed boiled milk from wet nurses in suitable complemental amounts.



Both of these infants were fed regularly from the first day, every two hours in the day and every three hours at night, their tolerance and ability to take measured amounts and their daily gain were the guides to feeding.



During the next six weeks Eleanor gained 2 pounds, 6 ounces, at the end of which she was taking 23 ounces in twenty-four hours, 460 calories, a quotient of 70 per pound.

During an equal period Susanne gained an identical amount, weighing 5 pounds, 15½ ounces at two months of age. Her quotient was somewhat higher throughout, reaching 76 per pound at two months.

It is probable that both infants would have thrived well on less milk and that other premature infants of the same weight might show digestive disturbances on so large an amount of food. Furthermore, the milk was not measured until after boiling, so that it was slightly more concentrated than normal breast milk. During this period both infants were given cod-liver oil 5 to 10 drops three times daily.

Chart 3.

Premature Twins.
Artificially Fed

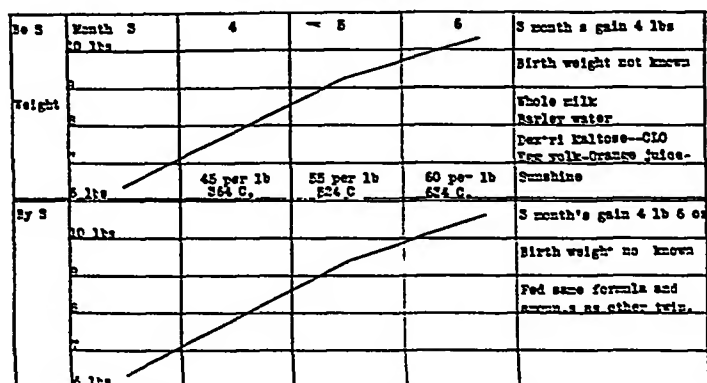


Fig. 218—Weight curves for the third to sixth months

Bernard S and Byron S were premature one month, their actual birth weight not known. They came under my observation when three months of age, having been fed condensed milk, without any gain for the previous two weeks, their stools had been dry and crumbling, rancid in odor.

Bernard gained 4 pounds in the next three months on boiled whole milk-barley-malt-sugar dilutions. He received egg yolk and orange juice during this period and was kept much of the time in the open air and sunshine.

Byron's weight ran parallel to his brother's continuously,

utilizing and tolerating identical amounts of food whose value increased from 364 to 634 calories daily (45 to 60 per pound)

These triplets, Nora, Wilma, and Ralph, were born within two weeks of their expected time, had birth weights of 6, 5, and 5 pounds. When seen by me at one month of age they weighed 6½ pounds, 5 pounds, 6 ounces, 4 pounds, 4 ounces, and had been fed on condensed milk. When asked if she had tried to nurse the babies the mother replied that as she had not enough

Chart 4

Premature Triplets
Artificially Fed

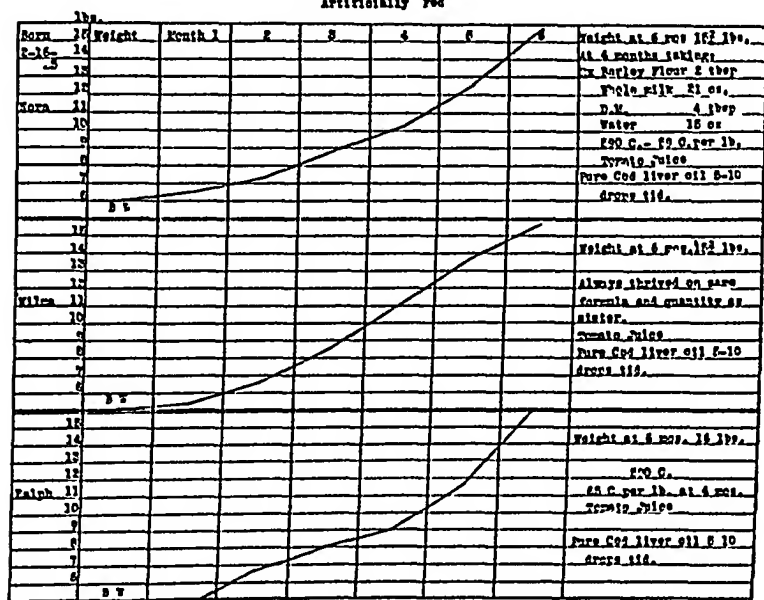


Fig. 219—Weight curves for triplets during first six months

milk for them all, she had discontinued trying to nurse any of them. The smallest and feeblest, the boy, was put to the breast and for two months succeeded in getting a small amount. It is a common occurrence for a mother to nurse the stronger of twins and put the weaker one, or "runt," on the bottle, because of the impression that he has no chance anyway. Obviously both should be nursed, and any preference should be toward the weaker infant.

The course of these triplets was uniform and without incidence. Feeding directions were carefully and intelligently obeyed by the mother without the assistance of a nurse. Simple whole milk dilutions were increased from time to time. At four months of age their energy quotient was still high, from 59 to 65 per pound. Wilma, who at the age of one month had a handicap of 1 pound, weighed exactly the same at six months as her sister, while Ralph with a handicap of 2 pounds at one month, weighed 16 pounds at six months, a trifle over the weight of the girls.

DISCUSSION

There has been marked improvement in the knowledge and care of premature infants in recent years. The recent work of Talbot and co-workers¹ on the basal metabolism of prematurity shows that the metabolism of the premature is lower for three months than that of the full-term infant. Because of lack of exercise, lower total heat production, absence of subcutaneous fat, inability to take the higher amounts of food required to replace the loss of heat—these factors make a handicap which only the stronger and better cared for infants can overcome.

It is necessary then to protect the child by sufficient external heat. This is best obtained in a warm room which is more difficult to obtain in the winter months. Overheating and lack of sufficient ventilation are the objections to most of the incubators which have been devised and most of which have been discarded for the warmed room or the simple basket heated by bottles or pads. It is seldom that the atmosphere needs to be above 90° F.

A minimum of handling in the early days is essential for the weakling, especially the infant weighing less than 3 pounds. Convenience of feeding and the toilet of the child should be included in the arrangement of the bed. Avoidance of infection is necessary, but exposure is common, especially because of the

¹ Talbot, F. B., Sisson, W. R., Moriarty, M. E., Dalrymple, A. J. *Amer Jour Dis Child*, vol 26, 29, July, 1923.

curiosity manifested toward these tiny infants by interested relatives, friends, and others

Cyanosis occurs as a disquieting symptom in the less mature infants. For this reason it is well to have at hand an oxygen apparatus as suggested recently by Bakwin.¹

Inability to nurse because of weakness, drowsiness, difficulty in swallowing, vomiting, embarrassment of respiration and occurrence of cyanosis from overdistention of the stomach and bowels, impossibility of securing breast milk—all these are factors which make up the hazards for the premature infant.

Breast milk in the markedly immature cases is an essential. This may be obtained by expression from the mother or other donor, and, as suggested by the speaker, may be boiled if the health of the wet nurse is not known. The mother's breasts should be stimulated by expression and suckling by a vigorous infant so as to conserve the secretion until the time that the premature can nurse.

As a suggestion for the amount of breast milk needed as a basis the following figures are given:

Breast milk, 54 to 67 calories per pound of body weight in order to gain. Infants at fourteen days, weighing from 3 to 5 pounds, to gain daily $\frac{1}{2}$ to $\frac{3}{4}$ ounce need breast milk 4 to 6 ounces. Infants at twenty-one days need breast milk 5 to 7 ounces. Infants at twenty-eight days need breast milk 5 to 8 ounces. Infants at thirty-five to sixty-three days need breast milk 6 to 10 ounces.

These are minimum amounts. If more is available and well tolerated, the daily quantity will exceed this.

In the first few days diluted milk may be given, but it seems wise to give milk undiluted at the earliest period possible because of the urgent food requirements. The interval of feeding is at two hours or thereabouts until the child can take larger amounts at a time, when the night feedings can be spaced wider, avoiding at all times excessive handling and disturbance.

Artificial feeding may be unavoidable in certain instances.

¹ Bakwin, Harry. Oxygen Therapy in Premature Babies with Anoxemia, *Amer Jour Dis Child*, xxx, 157, 1923.

Peptonized formulas, such as suggested by Hess¹ in the use of chymogen milk, will be successfully used in the stronger infants

Because of the fact that premature infants are potentially if not actively rachitic, the administration of cod-liver oil and egg yolk is of theoretic and practical benefit at the earliest age tolerated. When begun a few drops at a time it is possible to increase it to the necessary amounts

¹ Hess, Julius H. Principles and Practice of Infant Feeding, 98, 1922

CLINIC OF DR DAMON WALTHALL

BELL MEMORIAL HOSPITAL, UNIVERSITY OF KANSAS

A CASE OF TETANUS, WITH RECOVERY

TETANUS, usually a rather rare infection in childhood, does, however, occur. In text-books this infection is accredited to the newborn, but in our present-day aseptic technic of obstetrics it practically never occurs. In the past two years 4 cases of tetanus have come in to our clinic. The youngest was twenty-one months and the oldest fourteen years. In all of these cases the tetanus infection was secondary to a primary accident. In one the infection followed an automobile accident in which the tibia was crushed and the muscles of the upper and lower leg were badly lacerated. This case recovered, and was reported by Sulzbacher in the Medical Record, May 7, 1920. The other 3 cases were puncture wounds, 2 of which were nails, and the third was glass. Of these, 2 died and the other is the case being reported here which made a very interesting recovery.

History—Earl Ward, Record No 11,169

A white boy nine years of age came to the hospital August 19, 1921 from central Kansas. The history of the family was normal. In the past the patient had had the measles, whooping-cough, scarlet fever, and the last winter a bronchitis, which caused some loss of weight. His general health aside from this had been good until two weeks previous to his entrance he stepped on a rusty nail in a cow and horse lot. This nail penetrated about 1 inch the sole of the left foot, some 2 inches in front of the heel and near the external side. Turpentine was applied to this immediately by the mother and it was poulticed the next day. One week later he saw a physician because his foot was still sore and the foot was poulticed again. The punc-

ture wound on the foot stayed much the same except some redness developed posteriorly to the external malleolus

Two days before entrance it was noticed that the boy could not open his mouth and that his neck was slightly stiff, but he complained more of it being sore. Except for a mild headache he said he was not in pain or very uncomfortable

During his giving of the history he complained of difficulty in breathing and he acted restless and ill at ease

Examination—An undernourished, tense boy lying in bed with his knees drawn up, and a mask-like expression on his face. The mouth could not be opened more than $\frac{1}{2}$ inch. Whenever he smiled or tried to speak the effort of this threw the rest of the muscles into a hypertonicity. The head could be turned in all directions, but with his hands he held and supported his head whenever he sat up or lay down. If he allowed his neck to bend freely or quickly it caused pain. The back muscles were tense, thus holding the back stiff, but there was no pain. The muscles of the abdomen were rigid, and the abdominal reflexes very brisk. All the tendon reflexes were exaggerated and when elicited caused the muscles to become tense and remain that way for some time. The hamstring muscles were in a very tonic state and kept the knees flexed all of the time. The heart, lungs, liver, spleen, genitals, eyes, ears, nose, and throat were normal. The temperature on admittance was $101\frac{1}{4}^{\circ}$ F, the pulse 120, and respirations 26. The blood-count was 4,300,000 red cells, 90 per cent hemoglobin, 16,800 white cells. The differential count showed 75 per cent polymorphonuclears, 2 per cent large mononuclears, 16 per cent large lymphocytes, 9 per cent small lymphocytes, and 1 per cent transitional. The urine was dark straw color, clear, acid reaction, specific gravity of 1024, a trace of albumin, sugar negative, microscopic examination showed some mucus and a few white blood-cells, but no casts.

Treatment—On the history and symptoms elicited the diagnosis of tetanus was established beyond a doubt. Owing to the fact that no prophylactic dose of antitoxin had been given and that the boy denied in his history ever having had asthma,

hay-fever, or any other sensitization symptoms we felt free to proceed with a large initial dose of antitetanic serum 5000 units were given intravenously and 15 000 units deep in the muscles of the afflicted leg, 1500 units were given each successive day for ten days, and then after a four-day rest this dosage was repeated again for three consecutive days. A total of 36,500 units of antitetanic serum was given.

In conjunction with this specific treatment chloral hydrate in 5-grain doses and morphin in $\frac{1}{8}$ -grain doses were given from once to four times a day to control the muscle spasms. After the sixteenth day this part of the treatment was discontinued. The foot was treated locally with free incision, hot packs, and hydrogen peroxid irrigations. Also supportive treatment of saline hypodermoclysis and proctoclysis in conjunction with a high caloric liquid diet by mouth, taken through a straw, was given. On the twenty-fourth day of the disease the orthopedic surgeon applied a splint to stretch the contracted Achille's tendon. The thirty-first day of illness this boy was walking everywhere and his neurologic examination was normal.

Summary—1 Every individual with a history of a puncture wound similar to our patient should have the benefit of a prophylactic dose of antitetanus serum. This should be the usual 1500 units regardless of the child's age, *z e*, see case report, "Tetanus with Recovery," Sulzbacher Medical Record, May 7, 1921.

2 Early recognition of symptoms is very important. If these symptoms of trismus and other muscle hypertonicity come on slowly and gradually, developing fourteen to fifteen or more days after injury, there is a fairly good chance for recovery. If the symptoms come on early after the injury and are fulminating in character it is practically impossible to obtain a recovery. In these fulminating cases a lumbar puncture and the use of a serum into the dura has been of no avail.

3 The muscle spasms must be controlled with morphin, gr $\frac{1}{8}$, chloral, gr 5, with bromids gr 5, given repeatedly up to 60 to 80 grains per day, and chlorotorm. These are the drugs of choice. Ether is absolutely contraindicated because it is

stimulating in its first effect and this increases the spasm just before complete anesthesia is reached

4 Persistent and continued use of antitetanic serum into the vein and also along the course of the nerve sheaths of the afflicted limb probably is the most important treatment of all. However, it should be used early during the first few hours of symptoms or before any symptoms appear as prophylaxis, if excellent results are expected

5 Rigid isolation procedures must be carried out for several reasons

- (a) To prevent passing the infection on to other cases
- (b) Also to keep the patient quiet and free from noise and any unnecessary moving about, as noise and movements are liable to precipitate spasms

CLINIC OF DR. HUGH L DWYER

CHILDREN'S MERCY HOSPITAL

CONGENITAL DEXTROCARDIA TRUE AND FALSE

CONGENITAL dextrocardia is an uncommon anomaly, although in the examination of large groups of soldiers it was found more often than our previous statistics indicate, and a most surprising feature is its existence without the knowledge of the individual

The displacement may consist of a simple twisting of the organ on its axis so that the lateral surfaces come to lie more anteriorly, or it may be displaced to the right by adhesions. When this condition exists without the transposition of any other viscera it is termed "false dextrocardia "

In the primary or true dextrocardia the heart is in the right thoracic cavity with apex directed to the right This is the mirror image of the normal and is usually associated with transposition of the abdominal viscera The cases we have for study illustrate both types

Case I False Dextrocardia —Albert L , three years of age, was brought to the hospital when he was three weeks old because of a "collapse of the lung " His symptoms were cyanosis and difficult breathing at certain periods throughout the day A fit of crying usually precipitated an attack

Examination of the chest revealed hyperresonance on percussion over the left side, and very distant breath sounds The maximum cardiac impulse was on the right side, at the border of the sternum in the fourth interspace The heart sounds were heard fairly well any place on the right side, and not on the left

The area of cardiac dulness extended more to the right than normal. The apex and base of the right lung revealed no abnormal breath sounds or percussion note. We interpreted the physical findings in the chest as a *misplacement* of the heart to the right, with a compensatory emphysema of the left lung.



Fig. 220 —False dextrocardia, apex directed to left. No transposition of other viscera.

The liver occupied the normal position in the abdominal cavity, the spleen was not palpable, and further physical findings were essentially normal.

Radiographic Examination (Fig. 220) —This revealed the dis-

placement of the heart to the right thoracic cavity. The apex pointed to the left and the organ maintained the proper relation to the chest wall. A feathery shadow in the right upper part of the thorax, continuous with the shadow of the great vessels, was interpreted as bands of adhesions pulling the heart to the right. The abdominal viscera were shown in their normal position.

Discussion—This patient has been under observation and his physical findings are essentially the same today as when we first saw him. There has been no return of cyanosis or difficult breathing and he seems to be under no handicap because of this anomaly. He is brought in today for an x-ray and electrocardiograph examination, and these show his present condition. There is better aeration of the right upper lung at this time and the evidence of "bands" is not so apparent. You will notice that he is of normal development, there is no clubbing of his fingers, no cardiac murmur, and that the systolic sound is heard best to the right of the sternum.

Case II True Dextrocardia—Ruth B, thirteen months of age, is brought to the clinic because of a "cold and fever."

History—There has never been any cyanosis or difficult breathing, and her only trouble has been an occasional digestive upset.

Physical Examination—She is a well-developed and well-nourished baby with an upper respiratory catarrhal inflammation and a mild degree of bronchitis. The heart sounds are heard best on the right side, the area of cardiac dulness extends beyond the right nipple line. The maximum impulse is in the sixth interspace in the nipple line on the right side. On the left side there is no cardiac dulness and bronchovesicular breathing is heard over the area normally occupied by the heart. There is no murmur.

The liver is felt on the left, and the spleen in the right appears to be moderately enlarged. She presents the ordinary symptoms of bronchitis and there is no symptoms referable to her transposition of viscera.

Radiographic Examination —Shows a complete transposition of thoracic and abdominal viscera (Fig 221)

Electrocardiogram —The electrocardiograph is the best means of differentiating between the true and false dextrocardia. Because of the rotation of the cardiac axis in true dextrocardia in



Fig 221 —True dextrocardia, apex directed to right and abdominal viscera transposed

Lead I all the normal waves are seen as the inverted image. Lead II corresponds to a normal Lead III, and Lead III to a normal Lead II. Many cases have been studied in true dextrocardia, but electrocardiograph studies of false dextrocardia have been fewer. In false dextrocardia there is no inverted image, and

there is little or no deviation from the normal tracing Our patient shows only a left ventricular preponderance Whether this has any relation to the heart displacement it is difficult to

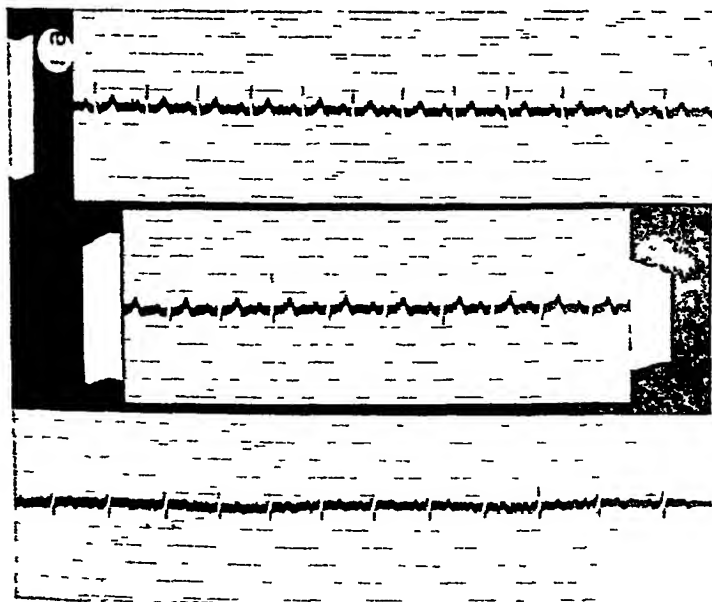


Fig 222—Electrocardiogram in false dextrocardia, showing only slight ventricular preponderance

say In infants and children, on account of the relatively thick walls of the right ventricle, there may be an electrocardiograph complex of right ventricle enlargement

A CHILD WITH CONGENITAL SYPHILIS AND DIABETES INSIPIDUS PRESENTING THE SYNDROME OF CORPORA STRIATA LESION

THIS patient, a girl eight years of age, came to the hospital eight months ago. Her chief complaint was intense thirst and polyuria. Her clinical picture has entirely changed since that time and now she presents motor disturbances, general muscular rigidity, mask-like facial expression, and tremor. This patient is of particular interest because of the fact that her nervous symptoms antedate her polyuria, and have become much more manifest after antisyphilitic medication, although her symptoms of diabetes insipidus have improved.

History—About four years ago she was treated for chorea which was so severe that morphin was necessary to control it. A year later an attack of appendicitis necessitated an operation, and shortly after it was noticed that she was consuming large amounts of water and passing 8 to 10 quarts of urine daily.

Physical examination at that time showed nothing noteworthy except slightly painful breasts and a local tenderness in the right inguinal region. She had been out of school a long time and it was difficult to judge her mentality. In the wards at night she would sleep very little, and would roam about putting water in other children's beds and similar pranks. During the day she would get her sleep.

Radiographic examination of the skull revealed a normal sella. Wassermann tests of the blood were positive, the cerebrospinal fluid was not examined.

Urine Colorless, specific gravity 1002, with no sugar, no albumin, and negative microscopic findings.

Hypodermic injections of pituitrin resulted in a diminished volume and a more concentrated urine. We interpreted her condition as diabetes insipidus probably due to syphilis, and she was discharged to the out-patient department for antisyphilitic medication. Five months later she re-entered for study of the effect of treatment and because she had developed a fine tremor and a stiffness of gait.

Physical examination She is a poorly nourished child, and moves about with a deliberate, stiff gait. The skin is dry and has a yellowish-brown tint, and the extremities cold. The speech is hesitant, seemingly a difficulty in getting started. The face has a mask-like expression, the mouth held open and there is considerable drooling. She holds food in her mouth for several minutes before swallowing. Both arms are slightly spastic, as also are the legs. This is more pronounced in the left arm. There is an irregular tremor of the intention type in both arms, more pronounced in the left. She walks unsteadily and there is a tendency toward retropulsion. You see if she is given a start backward she will go 20 feet without recovering her equilibrium. The tendon reflexes are normal.

Eye examination Fundi are normal with the exception of slightly pale disks. There is contraction for form and colors, slightly more marked on the temporal side in both eyes.

Blood The chemical blood findings were within normal limits. The Wassermann test is positive. The spinal fluid has been examined twice during the past month, and is clear, not under pressure, negative for globulin, normal cell content, and gave a negative colloidal gold test.

Urine After five months of arsphenamin and mercury medication her urine volume decreased from 6 or 8 to 3 liters a day, and has continued to decrease until now there is no abnormal thirst or polyuria. The specific gravity runs from 1002 to 1012 and has always been free from sugar, albumin, and casts.

The effect of pituitrin intramuscularly on the volume, sodium chlorid and urea excretion of the urine, is shown in Tables 1 and 2.

TABLE 1

EFFECT OF PITUITRIN ON URINE VOLUME				
Date	Intake	Output	Specific gravity	
9/26	3100	3300	1002	
9/27	3250	2900	1002	
9/28	2100	2100	1008	1 c.c. obstetric pituitrin
9/29	2100	1700	1012	" " "
9/30	2800	2600	1002	
10/1	2400	2820	1004	

TABLE 2

EFFECT OF PITUITRIN ON WATER, SODIUM CHLORIDE, AND UREA N EXCRETION
IN HOURLY SPECIMENS

Hour	Volume c.c.	Specific gravity	Urea N		NaCl	
			Per cent	Gm.	Per cent	Gm
6-7	360	1001	0.075	0.27	0.08	0.29
7-8	380	1001	0.095	0.36	0.07	0.27
8-9	240	1001	0.09	0.22	0.17	0.42
9-10	100 ¹	1010	0.28	0.28	0.18	0.18
10-11	62	1014	0.41	0.26	0.12	0.07
11-12	87	1016	0.65	0.54	0.08	0.07
12-1	120	1016	0.44	0.53	0.14	0.17
1-2	135	1010	0.43	0.56	0.13	0.17
2-3	165	1012	0.50	0.83	0.09	0.15
3-4	210	1002	0.16	0.33	0.06	0.13
4-5	200	1002	0.18	0.36	0.18	0.36
5-6	200	1004	0.20	0.41	0.14	0.28
Day,	2410			4.95		2.56
Night,	510		0.12	0.61	0.06	0.31
Total,	2920			5.56		2.87

¹ 1 c.c. pituitrin at 9:30 A. M.

There is a diminution of the salt excreted and of the total volume of urine, and acting somewhat slower, an increase of urea. Because of the yellowish-brown skin in the presence of the diabetes the possibility of some endocrine imbalance must be thought of. In certain endocrine disturbances it is known that the use of adrenalin intramuscularly produces a prolonged blood-sugar curve. This patient was put to that test at the height of her polyuria, but there was no deviation from the normal curve.

In some studies on diabetes insipidus an increased sugar tolerance has been found. Table 3 shows rather a normal tolerance in our patient.

TABLE 3

GLUCOSE TOLERANCE TEST—2 GM. GLUCOSE PER KILO BODY WEIGHT

	Mg. per 100 c.c.
Control	91
First hour	196
Second hour	121
Third hour	89
Fourth hour	89

Lumbar puncture has been found to have a favorable influence on the thirst and polyuria. In our patient two punctures were without noticeable effect.

Comment. To sum up our findings, we have a girl with a history of severe chorea, who came to us passing 6000 c.c. of urine a day. She was of queer temperament, was thought to be mentally retarded, but showed no evidence of organic nervous disorder. The blood Wassermann was positive, and she was given eighteen doses of arsphenamin alternated with mercury, over a period of five months. The urine volume decreased to 3000 c.c. a day and a fine tremor and stiffness of gait developed while she was on the antisyphilitic treatment. For the past six weeks she has been in the hospital, and with no treatment the diabetes insipidus has gradually disappeared. But the signs of organic brain disease are progressing.

The limbs are stiff, more marked on the left side, the left arm is held flexed to the side when she walks. There is disturbance of equilibrium, although she is able to walk about the ward, the face is set, drooling, difficult swallowing, and difficult speech are present. She is unable to feed herself on account of the tremor. There is apparently no pyramidal tract involvement, the reflexes are not increased.

The patient presents a syndrome that is associated with lesions of the corpus striatum. In juvenile paralysis agitans as described by Hunt there is rigidity with tremor, without choreiform movements, it is progressive and leads to speechlessness, and the reflexes are normal.

The polydipsia and polyuria in our patient may have been due to syphilis, but there is not much evidence of this. A syphilitic meningitis involving the pituitary body cannot be positively eliminated on account of the negative spinal fluid findings, because the fluid was not examined until after the antisyphilitic treatment. In view of the fact that symptoms of organic brain disease have developed it is probable that a lesion in some other part of the brain was responsible for the diabetes. It is a question whether the same lesion is responsible for both the present nervous symptoms and the diabetes, and whether the lesion is one of syphilis or not.

DEVELOPMENTAL DEFECTS OF THE SKULL ACRO- CEPHALY (OXYCEPHALY) AND ANENCEPHALY

DEFECTIVE development of the cranium may arise from widely varying factors. Before presenting our 2 patients it may be well to review the more common abnormalities.

The most common is failure of the sutures or fontanels to unite, or a delay in the normal ossification. This is frequently manifested in severe grades of rickets, in which the late closure is due to a faulty deposition of calcium salts. Late closure of the fontanels and sutures also occurs in hydrocephalus due to the intracranial pressure. A dystrophy of the cartilage of the body, as is found in the achondroplastic dwarf, affects the bones of cartilaginous origin at the base of the skull with the resulting large, brachycephalic head, with flattening of the bridge of the nose.

In congenital idiocy due to lack of brain development from intracranial hemorrhage or other obscure cause the openings of the skull may unite before normal growth is attained. This results in the microcephalic skull and is thought to be secondary to the abnormal brain growth. One of the patients we have for study today, I believe, falls into this group.

Case I—The patient is a girl one month old who was born with this peculiarly shaped head. Physical examination shows no abnormality except that of the head. She is not well developed, being much smaller than the average year-old infant, her heart, lungs, and abdominal viscera apparently are normal. There is no rigidity of the limbs and her patellar reflex cannot be elicited. The baby takes very little food, but maintains a fair state of nutrition, and rarely cries. There is great difficulty in feeding her because of strangling spells that are induced at swallowing. Swallowing seems to be her chief difficulty. Occasionally throughout the day she has these spells, in which there is rhyth-

mic contractions of the muscles of the neck, dilation of the veins of the head and neck, and the chin is brought down on the chest. These seizures also occur four or five times a day apart from the feeding time and last about one minute.

The skull has a cephalic index of 92 (breadth divided by length $\times 100$). The face is flat and broad and the skull slopes abruptly from the hairline on the forehead backward and down-



FIG. 223 —The microcephalic skull of anencephaly

ward to the occipital bone, and at this juncture there is a thick bony protuberance. All sutures and fontanels are closed. The ears project upward almost to the top of the head.

The mouth is open continually and the hard palate is not unduly high. There is never an expression of pleasure or displeasure unless the rare "crying spell" can be so interpreted. The eyes do not follow an object and they do not seem to focus.

on anything but maintain a continual blank stare directly in front

The radiogram shows a marked density of the entire skull. The uppermost part of the parietal suture is discernible.

Discussion—The condition is probably one of anencephalus. In some descriptions of anencephaly the cerebral hemispheres were missing, but the structures at the base of the brain, the basal ganglia, and cerebellum were present. This patient conforms to this description in so far as we are able to judge by the physical appearance and radiogram.

Case II—The next patient, a girl eight years old, presents a very high vertex, short anterior posterior diameter, a marked degree of exophthalmos with defective vision. This condition is congenital.

Physical Examination—It may be briefly stated that there is no abnormality of extremities, heart, lungs, or abdominal viscera. Her mentality is apparently normal and she progresses satisfactorily in a special class. The lower jaw is prognathic, the face short and wide, the veins of the scalp dilated, and there are no openings in the bony skull at the regions normally occupied by the fontanels. A slight ridge can be felt along the metopic suture ending on the vertex. Another bony ridge runs from the vertex along the sagittal suture to the occipital ending in a bony protuberance. The eyes present a buphthalmos, the cornea and sclera are normal, the pupils react normally, and there is optic atrophy, more marked on the left eye. The transverse axes are inclined outward and downward. The vision is 10/200 in the right eye and 15/200 in the left eye.

The radiogram shows very nicely the atrophy of the inner table due to the pressure of the convolutions of the brain, the putty-finger impressions. The highest point of the skull is in the region of the anterior fontanel. The sella is ill defined. The Wassermann test is negative. This is a classical case of acrocephaly.

Discussion—Various theories have been advanced to account for this abnormal development. The condition probably has

no relation to syphilis, so-called fetal rickets, or disease occurring in intra-uterine life

The condition is due to the premature ossification of the sutures. In brachycephalic heads, such as our patient has, the coronal and lambdoid sutures ossify and the head grows toward the vertex. The deformity is sometimes called tower-head and steepleskull. When the sagittal suture is the one to ossify

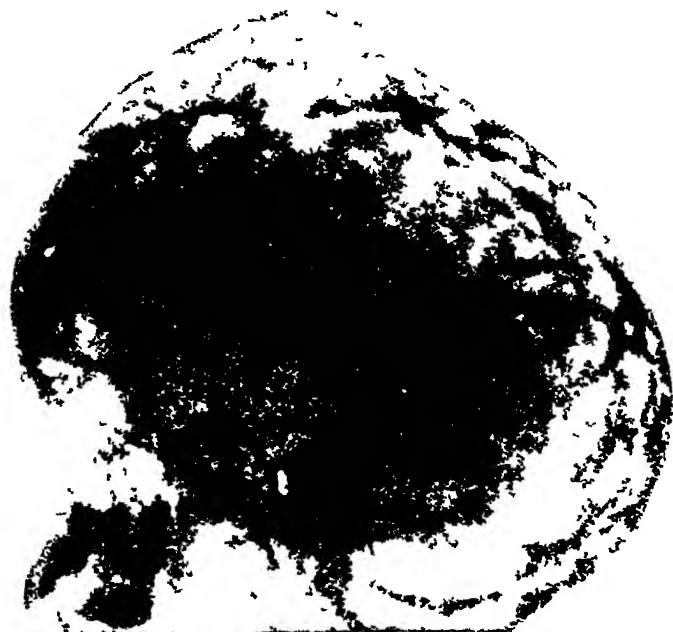


Fig 224 —Acrocephaly showing convolitional atrophy of bone

early, the head grows in a long anteroposterior diameter, giving rise to scaphocephaly

Park and Powers have come to the conclusion that the premature synostosis is due to some factor inherent in the bone and that this factor is present in the blastemal stage of development. The frequent combination of acrocephaly with syndactylism, and the familial incidence in several reported cases led them to this conclusion

Decompression operations have been advised for the patient, and probably is the only way progressive intracranial pressure could be relieved. Unless there was an associated hydrocephalus it is difficult to see how spinal puncture would be of any avail. Our patient is progressing in a special school and is enjoying life among her playmates with similar afflictions, so probably no treatment will be necessary.



THE TREATMENT OF SYPHILIS

FROM time to time some one suggests a "standardized" plan of treatment for lues, but in this, as in dealing with other more or less theoretic propositions, we seldom get beyond the point of suggestion

In no disease is early and intensive treatment more essential, and in few diseases is it more often neglected

There are several reasons for this, but the principal one, in my experience, is that nearly every medical man, no matter what his training, or lack of training, considers himself perfectly capable of successfully combating syphilis

Misdirected or insufficient effort is the cause of failure in some instances, unbridled enthusiasm, and inconsistency in others. It is not at all uncommon for one to encounter a case of advanced infection, probably with beginning tabes, in which the patient has been relying wholly upon $\frac{1}{4}$ grain of yellow iodid of mercury, after each meal, for a decade or longer. He had been assured by his doctor that this was all the treatment that he would ever need! On the other hand, we not infrequently see patients who are blindly and blissfully going their way, imagining that all is well after having received a dozen intravenous injections of neo-arsphenamin, and a few doses of a soluble mercurial by the same route, from some "intensive" enthusiast. Fortunately, both the medical profession and the public are awakening to the fact that syphilis is a serious disorder, and one which can be eradicated only by persistent and conscientious treatment

In the successful management of a case of syphilis the education of the patient is an important factor

Daily care of the teeth and gums, regular exercise, frequent or occasional hot baths, abstinence from stimulants, care in the promiscuous use of tableware—all of these are essential to the comfort and welfare of the infected individual and the safety of his associates.

The benefit to be derived from visits to the various watering-places is questionable. The skin and the kidneys should be kept active and in good condition, but one can drink water and take hot baths just as well at home as at Aix les Baines, and traveling is usually accompanied by irregular hours, and the ingestion of more or less strange and indigestible food.

In addition to these drawbacks some patients imagine that even the atmosphere of one of these so called "health resorts" is antisypilitic in character, and in consequence, they are very liable, during or following their visit, to altogether neglect the specific medication which is the only thing that will bring about a cure.

In attacking the *Treponema pallida* reliance must be placed upon mercury, arsenic, and, possibly, bismuth. The value of the last named drug is still in question.

Iodin is not a spirocheticide, although it is an invaluable adjuvant to the active preparations.

Mercury may be introduced into the body through a number of different channels—by the mouth, the lungs (by inhalation), the skin (byunction and by vaporization), subcutaneously, intramuscularly, and intravenously.

In my own experience, the two most dependable routes are the intradermal (byunction) and the intramuscular. If the drug must be given by the mouth, I prefer to prescribe it in the form of mercury with chalk (*hydrargyri cum creta*).

While mercury is probably our most valuable remedy in syphilis, it is, unfortunately, a kidney irritant. Schamberg and his associates have demonstrated, however, that when administered byunction it is least liable to cause nephritis.

It was formerly thought that calomel ointment was as efficient as mercurial ointment, but Cole and his co-workers showed by practical experimentation that calomel mixtures are

absorbed very poorly, and sometimes not at all, by the unbroken skin. Consequently, dependence must be had on unguentum hydrargyri, or one of its modifications, such as mercury with olive oil.

Personally, I have great confidence in mercurial inunctions and I believe that if faithfully employed they constitute one of the very best methods of treating syphilis.

In their employment, however, a frequently neglected but vitally important factor must always be considered—the co-operation of the afflicted individual.

Probably one patient in a hundred can be depended upon to rigidly follow the instructions of the medical advisor; the remaining ninety-nine will faithfully persist, for about a month, or until the cutaneous disfigurement begins to abate, and then they will gradually lengthen the periods between inunctions, until the treatment becomes farcical.

To simplify the matter for them is useless. It is quite probable that the daily application of from 3 to 5 grams of mercurial ointment to the soles of the feet, over the period of a year, or a year and a half, will bring about a cure in a considerable percentage of cases. The elements essential to ready absorption, heat and friction are already present, but I have found that few patients can be depended upon to carry out even this simple procedure.

For intramuscular injection either soluble or insoluble preparations may be used. The soluble ones, and particularly the bichlorid, which is a great favorite with Stokes, are cleanly and easy to manipulate, but absorption is so rapid that the injections must be made at twenty-four- or forty-eight-hour intervals, and this is impracticable unless the patient is under daily observation.

In the majority of instances the insoluble salts are to be given the preference. Calomel, in suspension, at one time was the favorite, particularly with Hallopeau and other French clinicians, but it is extremely painful, and unless carefully employed, is liable to give rise to salivation.

Lambkin, Fordyce, Pollitzer, Reasoner, and other men of

wide experience, speak highly of metallic mercury, in the form of gray oil (the oleum cinerum of Lang). It should be injected with a tuberculin syringe in order to secure accurate dosage and Fordyce's formula is best

	Parts
Redistilled mercury	30
Lanolin	45
Olive oil	75
Chloretone	15

Liquid petrolatum and vaselin should never be employed as vehicles. One of the most essential qualities of a vehicle for intramuscular use is absorbability, and as Weidman and a number of other pathologists have shown, mineral oils are not absorbed when injected into the tissues. Paraffinomas usually result. In 1915, 2 surgeons reported a series of tests on the antiluetic effects of mercury salicylate, with especial reference to its effect on the Wassermann test. Liquid petrolatum was the medium employed in the salicylate suspensions. They found that the injections had little effect serologically. Under the circumstances, it is a wonder that there was any resulting benefit at all.

Hazen, a syphilologist of excellent judgment and international reputation, is a strong advocate for mercury salicylate, and my experience parallels his. After giving almost every new preparation that has been suggested a trial, I invariably return to the salicylate. Hazen employs camphor and guaiacol as local anesthetics. I prefer anesthesin.

	Parts
Mercury salicylate	2
Anesthesin	2
Lanolin	4
Olive oil	30

The mixture is shaken, and from 10 to 15 drops injected into the buttock, twice weekly.

The injections give rise to very little discomfort, although in treating women care must be taken to lodge the dose in the gluteal muscles, otherwise it may become deposited in the thick layer of fat and cause pain and, possibly, become encysted.

It must always be borne in mind that absorption is slow.

(Schamberg, Kolmer, and Raiziss have shown that it is about 1 per cent a day), consequently care must be exercised to prevent the mercurial from "banking up" to a point where salivation may ensue

In order to guard against the injection of material directly into a vessel, with the possibility of thrombosis and embolism, the syringe piston should always be withdrawn for a centimeter or two, after the needle is inserted, and before the barrel is unloaded. If the tip of the needle is in a vessel, blood will of course rush into the barrel.

Arsphenamin and its weaker sister, neo-arsphenamin, have established for themselves a permanent place in the therapy of syphilis. While of less value than it was at first thought they would be, as symptomatic remedies they are both powerful and dependable.

Few syphilologists place their entire trust in the arsenicals, however, and, personally, I am of the opinion that mercury stands at the head of our list of antisypilitic weapons.

Fordyce and his associates, I. C. Sutton, and others in this country, speak very highly from the benefits to be derived from the use of silver arsphenamin.

While neo-arsphenamin, because of its ready solubility is extremely popular, its therapeutic efficiency is generally conceded to be far inferior to that of arsphenamin. Owing to the ease with which it can be prepared for administration, however it is very widely used.

The comparative value of the various methods of administering arsphenamin and neo-arsphenamin has long been a moot question. When first introduced by Ehrlich it was injected subcutaneously. Because of the pain and frequent resultant sloughing, however, soon afterward the intramuscular route was selected. The Alt-Lesser technic was the most popular, and the thirty or more cubic centimeters of solution, generally highly alkalinized, by guesswork and a 14 per cent mixture of sodium hydrate injected directly into the lumbar muscles or the buttocks. While this process of intramuscular medication was very efficacious, few patients could be persuaded to receive more than

one dose of the drug, and it was mainly to obviate this discomfort that the intravenous route was adopted.

By using this route one might not wholly get rid of tissue irritation, and even tissue destruction, but the patient escaped physical pain, and could be induced to take as many injections as his physician saw fit to give him. The fact that too frequent dosage sometimes gave rise to epilepsy, wide-spread thrombosis, hemorrhagic encephalitis, and hemorrhagic nephritis (Harrison), however, has never been sufficiently emphasized.

Fleig maintains that the therapeutic activity of the arsenobenzol compounds is "a function of their stay in the organism, and in inverse ratio to the rapidity of their elimination," and Brocq, the dean of Continental syphilographers, says, "Most of the recent investigators seem to show that the arsenical preparations introduced into the human economy by the intramuscular route or subcutaneously are eliminated by the excretories with infinitely less rapidity than when they are introduced into the veins. Their action by the former method of introduction appears to be more continuous, less powerful, more profound, so to speak." Harrison and Leonard conclude that "the intramuscular route gives the best results."

Craig found that one dose of arsphenamin properly administered intramuscularly was equivalent to two or three given intravenously, and Harrison, who is probably our foremost advocate for intramuscular injections, makes the percentage even greater.

Fordyce and Rosen employ neo arsphenamin intramuscularly as a routine measure in the treatment of syphilitic infants, and Schamberg also recommends it for this purpose.

Like most other syphilologists, I at first used the subcutaneous route, then the intramuscular, and then the intravenous. Any man who has had surgical training, however, can recall numerous instances in which untoward results have followed the intravenous injection of so innocent a preparation as decinormal salt solution.

And when realizing the usual character of the mixtures which enter the vein in arsphenamin medication by this route,

one can appreciate the chances for trouble that the patient almost invariably takes. If the solution escapes into the perivascular structures, tissue injury of varying degree, from cellulitis to gangrene, results. After a few injections into a single vein obliterative phlebitis commonly closes the passage and a new port of entry must be sought.

In my opinion, the only thing that saves the lives of the majority of patients who receive intravenous injections of arsphenamin and neo-arsphenamin is the rapid dilution of the irritating solution by the blood-stream. Even then, more or less endothelial injury is bound to occur. The fact that the patient experiences no pain is of little moment, the risk and the harm are there, nevertheless.

In addition to this vitally important question of trauma, one must also consider the comparative effects of transitory and of prolonged exposure of the treponema to arsenic. When thrown directly into the blood-stream, the arsenic remains in the body only for a few hours, as compared to days when it is injected intramuscularly.

While the theoretic question of arsenic-fast and mercury-fast organisms is still an unsettled one, I do not think that any one will dispute the fact that if temporary exposure to arsenic is detrimental to the health of a spirochete, prolonged association is liable to prove even more lethal.

For these two reasons I have, during the past ten years, depended wholly upon intramuscular injections of arsphenamin in those cases of syphilis in which I considered the drug indicated.

About two years ago, acting on the suggestion of my friend and former student, Dr. Steven Ragan, who served as an assistant to Colonel Harrison during the late war, I tried the intramuscular injections of neo-arsphenamin, but in my hands the ensuing pain was so severe that few patients would submit to more than one treatment.

The technic of the arsphenamin injections is very simple and can be carried out by any physician. The discomfort is but little greater than that following the use of the insoluble mercurials.

All instruments and utensils, and the 4 per cent aqueous solution of sodium hydrate (which is preferable to the stronger solution, because more readily manageable), are sterilized by heat

The arsphenamin is dissolved in 6 c c of sterile water by the aid of rough-surfaced glass beads, and 4 drops of a 1 per cent alcoholic solution of phenolphthalein added, as an indicator

So long as no alkali is present, the mixture can be shaken as vigorously as desired without fear of oxidation. The freshly boiled solution of sodium hydrate is then added, drop by drop, with a pipet, meantime gently agitating the mixture, until the resulting emulsion is slightly, but permanently, pink in color. I have found it best to not carry the alkalization too far. It does not increase the value of the remedy, and it does tend to render it more irritating to the tissues.

The mixture is then drawn into a glass syringe, to which is attached a needle at least 2 inches long, and injected into the gluteal muscles, care being taken to place it in the middle of the muscle mass. The injections are repeated once every four weeks, four injections forming a series. During three weeks of each interval mercurial medication is employed, with iodids as indicated.

Negative blood tests over the period of one year in which no medicine is given, together with negative spinal fluid, and total freedom from gross clinical manifestations, is requisite for a discharge. Each patient is urged to undergo two blood examinations a year, by a competent serologist, for the first five years following discontinuance of treatment.

In an experience covering several hundred cases I have learned to place great confidence in this plan of treatment, and it is for this reason that it is presented here.

CLINIC OF DR CHARLES C DENNIE

CHILDREN'S MERCY HOSPITAL

HEREDOSYPHILITIC TWINS

CONGENITAL syphilis in twins is of rather rare occurrence. Jeans, of St Louis, has made some rather interesting observations which we have been able to confirm in our clinic at the Children's Mercy Hospital. This paper is based upon the observation of seven sets of twins.

The course of acquired syphilis is tortuous and uncertain. We have to deal with a disease which in its untreated course has periods of activity and periods of quiescence. The four most potent factors which bring about these phenomena are (a) The natural resistance of the individual to the disease, (b) the virulence of the disease, (c) the age of the patient, and (d) the incidence of other intercurrent diseases.

Unless these factors are kept constantly in mind it is very difficult to understand some of the almost unexplainable vagaries of syphilis. Congenital syphilis has still more factors added to cloud the course of the disease. First, one or both of the parents are suffering from this disease at the time of conception, and will from their own deficiencies add a sinister influence to the impregnated cell and second, the treponemata in greater or less numbers will harass the new life from its beginning.

The physical condition of the parents at the time of conception certainly will have a direct and powerful influence upon the offspring. If the disease of the parents is simultaneously at low ebb, it is quite possible that this issue may be both physically and serologically sound, or show mild evidence of the disease late in life. If either of the parents suffer a strong recurrence the resulting child is nearly always a marked congenital syphilitic.

even though the parents are suffering from late lues. Thus it often occurs that the first 3 or 4 children in a syphilitic family are apparently free from the disease, and the last child shows marked evidence of involvement, or it may be that the first and last children are physically unaffected and the intermediates bear the brunt of the infection, or the first children will be badly involved while the last apparently escape.

A careful physical examination of the parents will often clear up an apparent mystery. Contrary to the older teachings,



Fig. 225—Twins I

a formidable percentage of mothers show either active evidence of syphilis or indications of past ravages. This is particularly true where the last child is the only one showing heredosyphilis. Nevertheless the first children show almost invariably strong serologic evidence of lues.

TWINS I (Fig. 225) —These infants were three months old when admitted to the hospital. They were not admitted because of any disease, but because of their peculiar appearance.

They bore many of the stigmata of mongolianism, such as square heads and faces, slanting eyes, short legs and arms, and broad, short-fingered hands. One (*A*) showed these characteristics stronger than the other (*B*), (*A*) had always been more rugged than (*B*), who died two months later. Active treatment produced no beneficial results.

Family History—The father and mother were both young, less than thirty. The twins were the only pregnancy.



Fig 226—Twins II

The mother was free from any signs of syphilis. The father had a large syphilitic ulcer on his leg.

Family Serology—Father, not taken. Mother, blood Wassermann ++++. Twins, blood Wassermann ++++

Twins II (Fig 226)—Twin girls nine years old admitted to the Out-patient Department because the smaller of the twins had not grown for three years. The larger (*C*) was 5 inches taller and weighed 14 pounds more than the smaller (*D*).

Family History—The father had died some years previously,

cause unknown The mother was living and well and showed no evidence of syphilis except a pupil on the left slow to light reaction No history of miscarriages

Scrology—Mother, B W +++++ Twins, B W +++++

Under antisyphilitic treatment the smaller twin gained both in weight and stature

Twins III.—Boys six weeks old admitted to the hospital because of skin eruptions Examination revealed one twin larger than his mate Pot-bellied, shriveled fingers with snuffles, large head veins, large liver and spleen, fissures and mucous patches about all mucous orifices, and a generalized maculopapular eruption

Family History—Mother dead, cause unknown Father living, apparently well Four older brothers and sisters not seen

Under treatment one twin did much better than the other Father moved to another state

Scrology—Father, B W +++++ Twins, B W +++++

Twins IV (Figs 227, 228)—Boys five years old, the one was admitted to the hospital because of sore eyes This trouble began one month previously with redness and photophobia

Previous History—Ordinary diseases of childhood One twin (L) had always had, since birth, a right-sided hemiplegia with a shortened tendo achillis Otherwise both had been in good health

Family History—The mother had one daughter of twenty years by a former marriage, a second daughter seven years old and the twins by a second marriage There was no history of miscarriages The seven-year-old daughter was without signs or symptoms of syphilis

Physical Examination of Affected Twin Square forehead, large head, small face, interstitial keratitis in left eye, saddle nose, lack of development of upper jaw, spastic paralysis of left arm and leg with shortening of tendo achillis, otherwise negative Diagnosis Congenital syphilis



Fig 227—Twins IV One twin showing many of the stigmata of congenital syphilis, the other twin apparently free



Fig 228—Twins IV, one year later The twins are now equal in size and the affected twin has shown great improvement The unaffected twin was not given treatment

Physical Examination of Normal Twin—A normal boy in every respect, much above the average boy intellectually and physically

Features in Common —Brown hair, blue eyes, same physical characteristics, speech, and same type of face except as the affected twin was modified by his disease

Serology —Mother, B W +++++ Daughter, seven years old, +++++ Affected twin, +++++ Unaffected twin, negative on repeated examinations

The cerebrospinal fluid examination

(a) Syphilis-free twin Wassermann negative, cell count 0, globulin 0, Lange's gold chlorid negative

(b) Congenital syphilitic twin Wassermann ++, globulin +, cell count 9, gold 1122100000

Discussion —Apparently split ovum twins, one bearing the major stigmata of congenital syphilis with a strongly positive Wassermann and cerebrospinal fluid, the other a normal healthy child with absolutely no sign of congenital syphilis and a consistently negative serology By some strange chance of fate the one has apparently escaped We have no theories as to why this happened, but simply offer it as a fact

Twins V —Boy and girl orphans seven years old, admitted to the house because the boy was suffering with eye trouble This trouble began six weeks previous to admittance The girl had never had eye trouble

Physical Examination, Boy —Square, low forehead too large for his face, interstitial keratitis of both eyes, fissures at angles of mouth, modified hutchinsonian teeth, extra cusps on six-year molars, scaphoid scapula

Physical Examination, Girl —Same as the boy except there was no evidence of interstitial keratitis Both had positive +++++ W R

Twins VI —Negro children six months old

Admitted to hospital because of malnutrition

Previous History —Cold in the head at age of two weeks Had not gained weight properly

Family History —Father deserted Mother apparently well

Boy —Larger than the girl Slight snuffles, abdomen large,

spleen and liver not felt Several small flat papules over scrotum and buttocks, general adenopathy

Girl—Smaller than boy, marked snuffles, fissures at corner of mouth, large spleen and liver, flat papules (numerous) over buttocks and vulva, mucous patches in mouth, general adenopathy

Serology—Mother, negative Twins, positive + + + +

Under arsphenamin treatment the syphilitic symptoms disappeared and the children gained in weight

Twins VII—Boys nine years old admitted to the clinic because of mental backwardness They had attended school three years, did not know the alphabet, nor could they distinguish one letter from the other

The family history was negative, as was the physical examination except for mental tests The boys were alert, well formed, and of more than average size

Serology—Mother, B W. + + + +. Twins, negative

While no evidence of syphilis could be demonstrated physically or serologically, they were given arsphenamin and mercury, with astounding results, in three months' time they could both read and write

Résumé—I One twin is always more affected by syphilis than his mate, even discounting the fact that one healthy twin is usually a little stronger than the other

II One twin may entirely escape the infection, while his mate has most of the major signs of it This can happen in single placenta split ovum twins

III That other abnormalities can occur in twins which is not connected with the disease, to wit, mongolianism

IV That congenital syphilis by affecting the endocrine system, produces marked differences in weight and stature, mentality, and stigmata, such as hutchinsonian teeth

V It produces marked change in the viscera, but not of the same degree

VI Children older than the twins show no stigmata, but do show markedly positive serology

THE PREVENTION AND CONTROL OF ACCIDENTS IN THE TREATMENT OF SYPHILIS

THE treatment of syphilis has been systematized to such an extent that it presents but few difficulties to the clinician. The preparations of arsenicals and mercurials have been refined with such care that one is seldom confronted by reactions due to toxic substances in their composition. But no matter how well the treatment is systematized or how free our preparations are from impurities, the individual peculiarity of the patient still remains, and technical accidents will happen to the most careful of practitioners.

1 Infiltrations from Arsphenamin Preparations.—Arsphenamin infiltrations are caused most frequently by the operator's needle passing through both sides of the vein. This can often be avoided by observing the following procedure:

(A) Always use a sharp ordinary No. 20 gage, long beveled needle, $1\frac{1}{4}$ inches in length. Grasp the syringe with needle attached, or the needle as the case may be, as one would grasp the bow of a violin, place the thumb of the left hand 6 inches below the sight of injection and make firm traction, lay the needle or syringe flat on the skin of the patient, and with one thrust pass through the skin and upper wall of the vein, by this method it is almost impossible to transfix the vein.

(B) If the tissue is being infiltrated with arsphenamin the patient will complain of pain. If the tissue is visibly infiltrated one of two methods are open:

Infiltrate the same area with 2 c.c. of a 10 per cent solution of sodium thiosulphate, in this instance most of the arsenic will in a few hours be converted into arsenic sulphid, which is comparatively non-toxic and non-irritating. Immediately after this antidote has been infiltrated into the injured tissue hot packs of a 5 per cent sodium thiosulphate solution should be applied for several hours. In most instances this will completely arrest even the most severe infiltrations. If in spite of this

treatment the severe infiltration still persists, multiple stab punctures should be made and the same dressing should be applied. If this is not done the area will often slough, and in some instances severe contractures will result.

2 Nitroid or Pseudo-anaphylactic Reactions.—The nitroid or pseudo-anaphylactic reaction is the most alarming crisis that occurs during or after the administration of arsphenamins.

Since 1920 these reactions are fortunately very rare, and their disappearance is probably due to the elimination of toxic substances from the arsenicals by the manufacturers. In the author's experience it has occurred only in adults. In ten thousand doses given to children over a period of four years it has not occurred once. This reaction is usually characterized by the following phenomena:

In many instances before all of the solution is administered the patient makes the statement that he feels very queer. The sclera become injected, the face is flushed, the veins of the head and neck are distended, and the pulse is full, bounding, and around 100, this may subside in a few moments leaving the patient a little weak, but otherwise well. In most cases, however, this flushing syndrome is immediately followed by extreme pallor, clammy perspiration, shallow respiration, and weak almost imperceptible pulse. The patient informs you that he is going to die and one is inclined to believe him. Still other symptoms and signs may present themselves, such as edema in various mucous orifices, urticarial wheals on the skin, asthmatic attacks and vomiting, with loss of control of the sphincters. In rare instances cerebral or spinal symptoms immediately present themselves probably due to an edema of the brain or cord.

While these phenomena are alarming, in most instances the patients recover. Cases in which death occurred have been reported. This condition is essentially the same as surgical shock and should be treated in a similar manner. The cause is problematic, but is usually due to toxic molecules in the manufacturer's product, which at first stimulates the suprarenals and later depresses them almost to the point of non-secretion.

Immediately inject intravenously 1 c c of a solution of 1 10,000 adrenalin chlorid to which has been added 1/100 gram of atropin sulphate Lay the patient down, cover him with blankets, place hot-water bottles or glass jars filled with hot water about him, and give by mouth 4 c c of aromatic spirits of ammonia in 8 ounces of hot water Repeat the adrenalin in ten to fifteen minutes if necessary and force hot fluids

This procedure rarely fails The clinician need not fear a similar attack if he wishes to give arsphenamin at a subsequent period

3 Immediate Central Nervous System Manifestations—

Case I—Congenital syphilitic aged five, the youngest of a family of 5, was given 0.2 gram of neo-arsphenamin from the same gross mixture that the other 4 had received treatment, one minute after administration and while yet on the table he lost consciousness His breathing became labored and stertorous The eyes diverged outward, the pupils were contracted, the pulse was full and bounding, the limbs were flaccid, 0.3 sodium thiosulphate in 5 c c distilled water was administered intravenously, with complete recovery in four hours He has been under observation for one year since that time and no untoward results have been observed It is probable that due to the rapid breaking up of the arsphenamin an edema was formed at the base of the brain

The rapid neutralization of this arsenical product with the sodium thiosulphate was probably responsible for his prompt recovery

Since the other 4 children were unaffected by the neo-arsphenamin from the same beaker, it is likely that this reaction was due to the condition existing within the individual

Case II—A patient of Dr F W McCallum was given 0.4 gm of arsphenamin, and twenty-four hours later developed cerebrocerebellar symptoms of the most alarming kind characterized by unco-ordinated constant, violent movements of which she was entirely conscious, but unable to control After twelve hours of this condition, which was uninfluenced by narcotics, the patient was given gas-oxygen anesthesia, a lumbar puncture

was done, and 30 c c of spinal fluid withdrawn. The symptoms immediately became less and ceased altogether twenty-four hours later.

4 **Arsphenamin Reactions Occurring Twenty-four to Seventy-two Hours After Administration**—(A) The so-called Jarish-Herxheimer reactions divided into three classes

1 Cutaneous manifestations, such as scarlatiniform or rubelliform rashes, papular rashes occurring on and often accentuating pre-existing early syphilitic eruption

2 Visceral manifestation which may attack any portion of the intestinal tract, urinary tract, or even the liver, followed by transitory slight jaundice

3 Central nervous system involvement, most frequently manifested by severe headaches probably due to cerebral edema, facial paralysis, or peripheral neuritis

These conditions with the exception of facial paralysis and peripheral neuritis are usually transitory and require no treatment, the facial paralysis is never permanent, but will take the same length of time for recovery that the usual Bell's palsy requires. If the headaches last for more than three days relief is promptly secured by one intravenous dose of 0.45 solution of thiosulphate.

(B) Prostration of more or less severe nature characterized by headache, vomiting, diarrhea, and rise in temperature

On close examination these patients will usually reveal an acute or chronic focal infection. The obvious thing, of course, is to remove all focal infections, such as teeth or tonsils, if possible, and never administer the arsphenamin if the patient is suffering from an acute infection no matter how slight. In this instance the patients promptly recover if food is withheld for twelve hours, and all fluids are given per rectum. The following twenty-four to forty-eight hours the patient should be given only solid foods with no fluids one hour preceding, during, or one hour after meals (after the method of Sippy). Between meals fluids, including alkaline water, should be given freely.

5 **Arsphenamin Dermatitis, Jaundice, or Both**—These

manifestations are the most severe and hold the gravest prognosis of all arsphenamin reactions

Predisposing Factors—(a) Individual sensitization of the patient to the arsenicals

These people usually develop their complications after the second or third dose

(b) Focal infections, teeth, tonsils, sinuses, peribronchial glands, chronic gall-bladder, appendix, or infected genito-urinary tract ¹

(c) Chronic disease of the great secretory or excretory glands, especially the liver

(d) The incidence of acute intercurrent disease

(e) The use of arsenic and mercury in large doses during the same course, or the use of large doses of arsphenamin at too close intervals ²

Warning Symptoms and Signs—(a) Itching of the soles of the feet and palms of the hands Generalized itching

(b) Rubelliform and scarlatiniform eruptions accompanied by moderate or severe itching

(c) Persistent headaches, nausea, and general sensation of ill feeling

(d) Loss of weight, with extreme nervousness

Types of Arsphenamin Dermatitis—(a) Mild, in which the scarlatiniform eruption is followed by branny scaling

(b) Moderately severe, in which the desquamation is like that of scarlet fever, including palms of hands and soles of feet

(c) Severe, in which the rubelliform rash is followed first by edema of eyelids and face, and a little later edema of the extremities, soon followed by profuse oozing and crusting of the entire body, duration from one to three weeks

The edema then disappears and a scaly, dry, pigmented skin results which lasts for months The sweat and oil glands regain their functions very slowly and sometimes not at all

(d) Very severe type, which not only shows the severe cutaneous involvement, but the tongue esophagus, and intestinal

¹ Stokes, Archives of Dermatology and Syphilology, January, 1923

² McBride and Dennie, Ibid

tract are also involved In this type the first symptoms appear in the mouth as an intense stomatitis and glossitis Such a case was referred by Dr W W Duke, of Kansas City

(e) Severe dermatitis with jaundice, nearly always fatal until the advent of sodium thiosulphate

Treatment—Since the cause of arsphenamin dermatitis has been demonstrated to be due to improperly split arsenical compounds stored in the liver, the logical treatment would be to neutralize these chemicals Such a method was reported by Dr W L McBride¹ and the author This method consists of the intravenous administration of sodium thiosulphate dissolved in 10 c c of distilled water given daily for four days in the following dosage 0.45, 0.6, 0.9, 1 gm The succeeding dosage to be governed by the condition of the patient Simultaneously 1 gram of sodium thiosulphate is given t i d by mouth By this method the course of the dermatitis is cut from six months to as many weeks Pusey, Ormsby, Mitchell, and others of Chicago, Stokes of Rochester, Wile of Ann Arbor, Schamberg of Philadelphia, Markley of Denver, Alderson of San Francisco, Hissen of Wichita, Duke of Kansas City, Milne of Kansas City, and many others have verbally reported its successful use McBride and the author have used it successfully in over 30 cases during the course of four years It is understood, of course, that the patient² is to be put on a low caloric diet with plenty of fluids A soothing ointment should be used externally, preferably a tragacanth emulsion of olive oil, daily exposure to sunlight is of great importance

Jaundice Unaccompanied by Dermatitis—In arsphenamin dermatitis and jaundice the injury to the kidney is, as a rule, negligible The liver suffers the brunt of the injury In cases that have gone to autopsy all degrees of liver injury from cloudy swelling to massive liver necrosis have been found All degrees of jaundice are seen ranging from yellow conjunctivæ to deep bronzing of the entire skin With but few exceptions these cases clear if put under the sodium thiosulphate régime

¹ Archives of Dermatology and Syphilis, January, 1923

² Smith cited (Lancet) by French, 1, 262, June, 1920

These exceptions are some of the cases in which the skin is almost black

Peripheral neuritis, myelitis, cerebritis Any one of these three may occur anywhere from two weeks to three months after intensive treatment with the arsenicals

All are slower to respond to treatment than the other conditions for the well-known reasons that edema has taken place. Nervous tissue does not take kindly to edema if it exists for some time, no matter what the cause, consequently, when the cause is removed recovery of nerve activity is slow. In one case of myelitis referred by Dr E Lee Miller an incomplete Brown-Séquard paralysis developed within twenty-four hours. This was ushered in by difficulty in urination which soon developed into complete suppression, complete loss of the use of the right leg and hyperesthesia, and partial loss of left leg with hypoesthesia, the area of hypoesthesia extended from above the twelfth dorsal vertebra downward. The patient was seen on the fourth day and started on intravenous sodium thiosulphate. In one week he began to move the paralyzed leg, and in one month was walking with canes, and completely regained the control of all his functions

6 Mercurial Stomatitis—The symptoms of mercurial stomatitis are so well known they need not be described here

Predisposing Factors—(1) Pyorrhea alveolaris. In practically all cases of Rigg's disease the Vincent spirillum and the fusiform bacillus exist probably as parasites

(2) Poor oral hygiene

(3) Tobacco

Treatment—(1) Care of the teeth and gums, through brushing, removal of deposits, and a chlorinated mouth-wash such as ash solution

(2) Intravenous use of sodium thiosulphate. In cases in which this régime is followed mercurial stomatitis promptly disappears

Acute mercurial poisoning from the intravenous use of soluble mercurials and the intramuscular use of salicylate of mercury,

probably the only non-soluble mercurial producing acute metallic intoxication

These cases are precipitate and are characterized by cramps, tenesmus, bloody stools, and prostration. Albumin, blood, and casts may be present in the urine. Sodium thiosulphate by mouth and intravenously is indicated, then signs and symptoms promptly disappear. This method is very successful in the treatment of individuals who have taken large doses of bichlorid of mercury.

Indurations and Abscess from the Intramuscular Administration of Arsenicals or Mercurials.—Painful indurated masses often follow this method of treatment. Hot saline packs applied for one hour, two or three times a day, will usually suffice. If the mass fails to disappear under this treatment and becomes somewhat soft, it should be immediately opened and drained. Prompt healing will result since these masses are usually sterile.

RESUME

(a) Sodium thiosulphate is the most successful neutralizing agent for mercurial and arsenical intoxication, no matter what the manifestation. It can also be successfully used in lead and bismuth or any of the heavy metals belonging to this group.

(b) Arsenical dermatitis and jaundice are preceded by certain signs and symptoms which should warn the clinician to discontinue the use of arsphenamin.

(c) If very intensive treatment is used, mercury and arsenic should not be used in the same course unless the patient is very closely guarded by frequent searching examinations.

(d) All solutions given intravenously should be filtered through a filter upon which the needle is directly fitted.

(e) Local or acute infections, intercurrent diseases, liver or kidney injury are contraindications to the use of arsenicals and mercurials.

The occurrence of one nitroid reaction in an adult patient does not predispose him to a second when arsenicals are again given.

CLINIC OF DR WILLIAM K TRIMBLE

BELL MEMORIAL HOSPITAL, UNIVERSITY OF KANSAS

NEGLECTED FACTORS IN THE TREATMENT OF SYPHILIS

THE 3 cases which I have to present today have been under observation for a number of years. They have been selected for the purpose of showing the importance of secondary factors in the treatment of syphilis—factors which are far too frequently disregarded in the care of the syphilitic patient.

The first case is a young man twenty-four years of age. He claims to have always been in perfect health and to have had no serious illness in his lifetime. As you see him now he is in good state of nutrition and is apparently in perfect health. In June, 1918 he came in with a healing genital lesion and with a flat, pigmented, macular eruption covering the arms, chest, and abdomen. The epitrochlears, postcervical, and inguinal lymph-nodes were palpable and distinctly enlarged. The teeth and gums were bad. Pus could be squeezed from about the gums. His pupils were equal and all reflexes normal. He had no headaches. The urine was negative and the Wassermann test 4 plus positive.

He was given 4 doses of neosalvarsan, 3.5 gm, followed by 20 grains of bichlorid of mercury in the muscle, 2 to 3 grains each week. No salivation and no albumin in the urine. He was told to consult a dentist who advised the removal of a number of teeth and treatment for pyorrhea. He refused to have this work done at the time. After two weeks' rest the above course of treatment was repeated. No further treatment was given and in six weeks his Wassermann was 4 plus positive. This course of treatment was repeated, followed in a few weeks by a nega-

tive test, but in three months without treatment it was again 4 plus. He was again given 20 grains of mercury and then given mixed treatment by mouth for three months. In the course of a few months his test was again 4 plus.

During the entire course of the treatment the patient was in excellent general condition, and save for the positive test might have been dismissed as so-called cured. Care of the teeth was now insisted upon. Four teeth were found with apical granulomas and were removed. The gums were treated. No further specific medication was given at this time. In a few months he reported a negative test. At present, nearly two years after treatment of the teeth and without specific therapy, his test is negative. Additional treatment has been advised, but not taken.

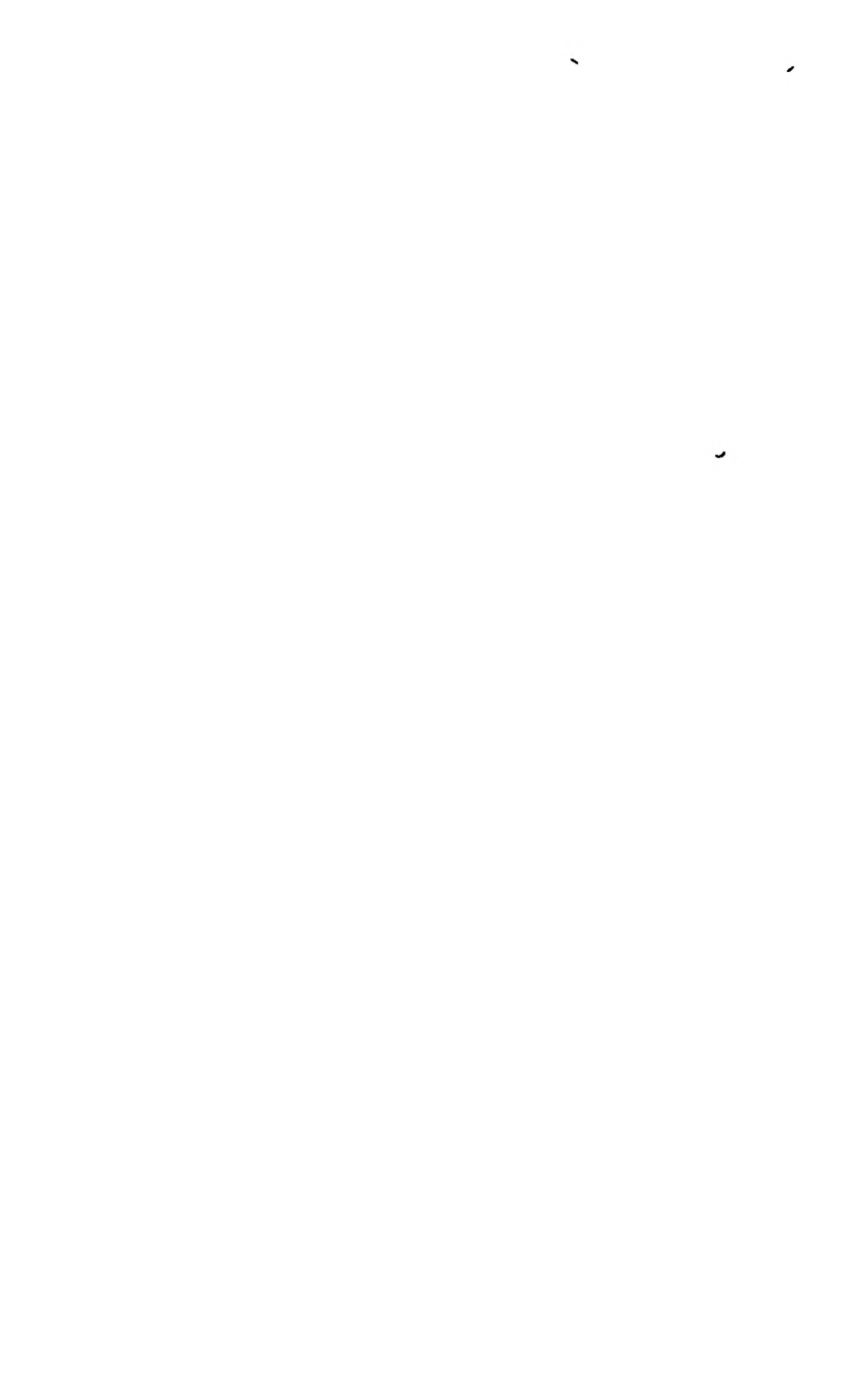
The second case, Mrs. C., consulted her physician because of extreme nervousness and insomnia. Her physician diagnosed nervous syphilis. Her Wassermann test was 4 plus. From her statement she must have received a good consistent course of treatment at the time. Her insomnia and nervousness completely disappeared and she was in excellent health for two years when these two major symptoms recurred. The Wassermann test was 4 plus positive. A spinal puncture was refused. Vigorous treatment relieved her of her symptoms in a degree only. An examination for focal infections showed the teeth unusually good, with the tonsils infected and the fauces red and dry. A mass was found in the left pelvis. Operation was advised and a simple cyst of the ovary of some size was removed. Following this her symptoms were greatly improved, but the insomnia returned. Her throat became sore and pus could be expressed from both tonsils. The tonsils were removed. Previous to the abdominal operation and the removal of the tonsils the Wassermann was 4 plus positive. Six weeks afterward the test was negative, although no specific treatment was being given during this time.

The third case, Mrs. H., in 1914 contracted, innocently, an infection on the tongue. She was given salvarsan and mercury by her physician over a period of eighteen months to two years.

She was in excellent health until 1920, when she developed a sore tongue, with flatulence, and was nervous and irritable. The tongue was red, fissured, swollen, and covered with flat serpiginous lesions. The tongue presented features of a typical late luetic glossitis. The Wassermann was 4 plus. Vigorous treatment removed her subjective symptoms, but failed to materially change the character of the tongue. The Wassermann remained positive.

Examination of the patient for focal infections failed to reveal any areas. She has a retroflexed uterus which is freely movable. Because of the flatulence she was given a test-breakfast and found to have only 6 points of free HCl, and after a full meal 10 points. This patient was given 20 gtts of dilute HCl with 5 grains of pepsin immediately after meals, with the dose repeated in thirty minutes. In a very short time the tongue had cleared and the flatulence and nervousness had disappeared. Her test became negative without further specific treatment. She has received some treatment since, however, and now has a negative test with no positive findings.

The outstanding feature in these cases has been the persistently positive Wassermann tests and symptoms without objective findings. A few years ago such cases might have been considered as being Wassermann fast and the patients given a very unfavorable prognosis. Every case of syphilis, regardless of the stage in which it is presented for care, should be closely inspected for focal infections or other defects, and these should be cared for as soon as it is consistent to do so. Since the damaging effects of long-continued absorption from focal areas of infection on the character of the blood-vessels, the heart muscle, and heart function, even in the lesser years of life, have been so clearly shown, may not the removal of these focal areas be a factor in reducing the incident of cardiovascular lues? Or, again, where the absorbed toxin is particularly selective for nervous tissue may not this also be a factor, where left untreated, in increasing the incident of neurosyphilis?



CLINIC OF DR. PAUL F STOOKEY

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CARDIOVASCULAR SYPHILIS

IN the light of our present-day knowledge of the vascular changes produced by the invasion of the heart and great vessels by the *Treponema pallida*, it is of intense interest to review the pathologic literature of the pre-Wassermann days. One is impressed by the accuracy of the pathologists in the recognition of syphilitic changes in the great vessels. Certainly the advent of the Wassermann and the discovery of *Treponema pallida* gave the clinician a clearer insight into cardiovascular diseases, and a careful study of such cases on the postmortem table has greatly enhanced our knowledge of the vascular manifestations of syphilis. If a degenerative process in the vessels is attributed to syphilis the *Treponema pallida* should be demonstrated in that tissue. Many of these problems have been definitely solved, some few require further investigation to definitely establish their relationship to syphilis.

When the organism infected with the *Treponema pallida* reaches that stage in the evolution of its syphilis that secondary manifestations occur, in short, when the *Treponema pallida* are disseminated from the local focus by the blood-stream throughout the body, which fact is announced by secondary manifestations and a positive Wassermann, then the heart and great vessels are involved—cardiovascular syphilis exists.

Erdheim reports the case of a man with secondary syphilis of six weeks' duration who suffered a violent accidental death. Microscopic examination of his aorta showed the characteristic round-celled infiltration with degeneration of the elastic tissue in the media, and the *Treponema pallida* were demonstrated *in situ* by Levaditi's method.

To the clinician, who is at best an occasional pathologist, the manifestations of syphilis of the heart muscle produce many perplexing problems. One must consider the damage done by the invader in the muscle tissue by its presence plus the manifestations of degeneration produced by the increased demand upon the heart muscle in aortic incompetency. The characteristic feature that is so striking in the manifestations of syphilis of the aorta unfortunately is not in evidence upon gross inspection of the heart. If the aorta shows the characteristic lesions of syphilitic degeneration of its media, one is led with considerable justice to assume that to a degree the existing cardiac pathology is due to the presence of syphilis. If the existing syphilis is of comparatively recent date, the aorta may show in gross examination an extensive involvement, while the cardiac muscle on gross inspection is apparently normal. More frequently the characteristic lesions are present in the aorta and the heart shows hypertrophy and a varying degree of fibrosis. To Homer J Wright, of Boston, and Warthin, of Ann Arbor, are due our present knowledge of the microscopic pathology produced by invasion of the heart muscle by the *Treponema pallida*. In Warthin's original article comprising a large series of cases, representing both acquired and congenital cardiac manifestations of the disease, the gross and microscopic findings are reported in detail. One of the most impressive statements embodied in his original report is the demonstration of the *Treponema pallida* in the heart muscle by the Levaditi stain in an organ that on gross examination showed no pathologic changes. This fact recalls to the mind of the clinician Fournier's assertion "that syphilis sleeps, it never dies." Warthin describes parenchymatous degenerative changes and a more chronic interstitial type associated with fibrosis, both types showing the presence of *Treponema pallida* by Levaditi's method.

A localized syphilitic process may attack the wall of the left ventricle and so damage the cardiac muscle that an aneurysmal dilatation of the ventricular wall subsequently develops in the damaged muscle. Microscopically the structure is that of a gumma.

That syphilis and aortic disease were frequently associated was a pre-Wassermann observation of the older clinicians. Our present conception of the pathologic changes characteristic of syphilis in the cardiovascular system dates from the original description of Doehle and Heller. Syphilis is described as a disease of connective tissue, the truth of such a description is well illustrated in the pathology of the aorta. The process is most marked in the beginning of the aorta, and the arch, being less in evidence as the great vessel reaches the diaphragm, where in the usual case the characteristic lesions disappear, the aorta in its abdominal part being smooth and glistening in appearance. This is in contrast to atheromatous degenerative processes which attain their maximum of development at the bifurcation of the aorta and show no special predilection for the arch. Exceptionally syphilitic disease with aneurysm is present in the abdomen, however, in a vast majority of cases the characteristic lesions are localized above the diaphragm. The gross appearance shows numerous depressions which are difficult to describe. Steork compares these depressions to the striæ of pregnancy present on the abdomen of the multipara. The comparison is fairly accurate both as to appearance and histologic pathology. Over these depressions the intima is of almost normal appearance, or, if the process is of considerable duration, the intima may show some attempt at compensatory hypertrophy. The depressions are produced by the rupture and disintegration of the elastic tissue in the media, each depression representing a potential aneurysm. The degeneration of the media also produces a wrinkling of the intima characteristic of syphilis. This fact is exaggerated in preserved specimens, and while it undoubtedly exists antemortem, the dehydration of the tissues after death intensify this characteristic manifestation. Calcification is never present, and if found represents an associated atheromatous degeneration. The aortic ring is generally dilated and frequently the arch shows dilatation of a variable degree, aneurysm may be present. The characteristic loss of elasticity that must be present when one considers the extensive degeneration of elastic tissue in the media may go

to explain the shortness of breath, pain, and mediastinal discomfort so prominent in the history of the early clinical cases of aortitis

Aneurysm develops in the depression formed by the rupture and disintegration of the elastic tissue. Occasionally the intima will be dissected up along with half of the media by the bloodstream and a dissecting aneurysm be produced.

A small round-celled infiltration with plasma cells and an occasional multinucleated giant-cell are found in the media and adventitia. The vasa vasorum show an extensive infiltration and marked deformity. If the elastic tissue is stained, one is impressed by its markedly degenerated appearance in the media showing clumps and interrupted groupings of degenerated elastic fibers with a repeated irregular interruption of continuity.

It is customary in the consideration of the pathology of cardiovascular syphilis to describe syphilitic pericarditis and endocarditis. I believe the endocarditis to be of secondary importance from both a clinical and pathologic standpoint. Clinicians and pathologists alike have long associated syphilis with the aortic valve. On postmortem examination the aortic valves are frequently sclerotic, slightly thickened, and generally incompetent. The ragged, irregular deformity of the valve, so characteristic of infective endocarditis, is always wanting. The valvular margins are smooth and the major parts of the incompetency is produced not by the valves, but by a dilatation of the entire aortic ring. Even in the presence of slight thickening and stiffness with adhesions between the valve cusps at their attachment to the aortic ring, all of which is generally present postmortem in the cardiovascular syphilitic, one must search further for an explanation of the entire lack of diastolic blood-pressure which is so often the outstanding antemortem clinical feature. In a given case who has lived for considerable time with a diastolic blood-pressure that cannot be read, one is impressed by the slight postmortem deformity in the valve cusps, and must conclude the incompetency is due to a large degree not to the deformity of the valve segments, but an incompetency

produced by dilatation of the entire aortic ring I believe that the association of syphilis and the aortic valve is produced not by the deformity of the valve segments, but by the degenerative process in the elastic tissue of the aorta, with dilatation of the first part of the aorta and the aortic ring

The importance of syphilis in association with angina pectoris has led to an extensive literature on the changes produced in the coronary vessels by syphilitic infection The process is identical with that occurring in the aorta As in the aorta, the process is one of elastic tissue degeneration The anatomic structure of the first two or three centimeters of the coronary vessels is similar to that of the aorta The media shows much elastic tissue at the origin of the vessels, hence the pathologic process with its predilection for connective tissue is to an astonishing degree confined to the first, second, or third centimeters of the vessels

The changes are often extensive and exactly similar in gross and microscopic appearances to those previously described in the aorta, complicated by the fact that the openings of the vessels are markedly constricted and deformed by the dilatation of that part of the aorta from which the coronaries arise Thus is produced a deformity that markedly interferes with the nutrition of the heart muscles This pathologic fact is frequently encountered in the postmortem examinations of cardiac syphilitics following sudden death

The calcification and obliteration of the lumen of the coronaries so frequently seen postmortem in anginal subjects is, in the light of our present-day knowledge, not attributable to syphilis While many of the cases presenting an obliterating endarteritis with calcification may be associated with syphilis, the presence of the calcification excludes the possibilities of attributing the existing pathology to a syphilitic degenerative process

Cardiovascular manifestation of syphilis occurs at any age, but is most frequent in young adults Males are afflicted with greater frequency than females, the ratio being four to one The negro shows a marked susceptibility Physical strain is a

frequently associated factor. The absence of the history of rheumatic fever or an acute infection is conspicuous in the history of every case. Clinically the findings vary over a wide field, in a beginning syphilitic degeneration of the aorta the findings are slight. The subjective symptoms are of unusual severity and include pain, precordial or mediastinal, frequently paroxysmal in character, which may be associated with dyspnea and is frequently nocturnal. Physical examination at this stage shows no inkling of the developing condition other than some slight anomaly of the aortic sound. Fortunately, the Wassermann is positive in a higher percentage of cases, and often gives the clinician a true understanding of a developing pathology. Subsequently, as the aortic valve becomes incompetent the symptoms are characteristic, the high pulse pressure, Corrigan's pulse, diastolic murmur, wide-spread arterial pulsation, most marked in the carotids, and the heaving impulse of the heart against the chest wall, all indicate an incompetent aortic valve. Pulsation at the right second interspace is frequently present.

The murmur and the blood-pressure are of special interest. At the London National Hospital for Diseases of the Heart the high systolic blood-pressure so characteristic of aortic incompetency is interpreted as an attempt to maintain an adequate blood-pressure in the important centers in the brain and not as a manifestation of peripheral arterial disease.

The same observers call attention to the marked discrepancy of the systolic blood-pressure in the leg and arm in aortic incompetency. Not infrequently the systolic reading in the femoral artery will be from 20 to 100 mm. of mercury higher than that obtained in the brachial artery.

The murmur is soft and blowing, diastolic in time, and occasionally difficult to hear. In my experience it can be heard over both the aortic and pulmonary area with equal intensity. One may be confronted by the murmur described by Austin Flint. Much has accumulated in the literature concerning this murmur and its mode of production. I have found it to present widely different characteristics in my cases. In the presence of an unusual murmur of difficult or impossible interpretation

one should turn to the pulse and blood-pressure for evidence of aortic incompetency, as an aorta so damaged as to produce this murmur has, in my experience, always been associated with the characteristic signs of aortic incompetency. The discussion of the physical diagnosis of cardiac disease and aneurysm does not fall within the scope of this paper. However, if the clinician will demand stereoscopic roentgenograms of the heart and aorta in every case of cardiac disease beginning aneurysm will be more frequently recognized. It is important to not only study the flat plate, but to look behind the aorta with the fluoroscope, which procedure, if adopted as a routine, will occasionally save a diagnostic error. The Wassermann is a valuable diagnostic aid and is, fortunately, positive in a high percentage of cardiovascular disease due to syphilis. However, it is not amiss for the clinician to recall that in the presence of aortic incompetency in a young adult who has never had rheumatic fever the therapeutic test is our most accurate method of establishing the presence of syphilis. In my cases of cardiovascular syphilis I have been impressed by the lack of clinical evidence of associated involvement of the central nervous system.

The clinician should recall that a syphilitic disease of the cardiovascular system is a progressive degenerative process and the prognosis is at best uncertain. One may, by careful consideration and survey of the history, duration, physical and laboratory findings, after the individual's response to treatment has been ascertained, hazard an opinion with a certain degree of prognostic accuracy, ever recalling that sudden death is a frequent termination of aortic disease. Cases presenting but few physical signs may rapidly progress in the face of treatment, develop angina, and terminate in death in an incredibly short space of time. In contrast to this, cases presenting a marked widening of the aorta, with a diastolic murmur, Corrigan's pulse, and cardiac hypertrophy may show marked subjective improvement under treatment, and lead an active and useful life over a long period of years.

Experience teaches certain prognostic facts that should be carefully considered in offering a prognosis in cardiovascular

syphilis Tachycardia in aortic disease of syphilitic etiology is generally indicative of a markedly degenerated heart muscle. Auricular fibrillation is not so common as in mitral disease, but once established is permanent, and an irregular pulse with positive clinical evidence of aortic disease offers a bad prognosis. Attacks of angina pectoris with pain radiating down the left arm to the thumb and little finger are forerunners of a sudden fatal termination. In marked contrast to this the clinician frequently encounters cardiovascular syphilitics with precordial pain, paroxysmal in character, which disappears under anti-syphilitic treatment. These cases that show marked improvement or complete recovery from pain, under specific medication, never experience the radiation of pain to the thumb and little finger, nor the impending sense of death so characteristic of the fatal cases of angina pectoris. The pain may be on exertion referred along the sternum into the neck, and of such severity as to totally incapacitate the patient subsequently to completely disappear under specific treatment. The age of the patient and the duration of the syphilitic process are to be carefully considered from a prognostic standpoint. Young adults respond to treatment to a greater degree than those advanced in years. The duration of the existing syphilis is a factor of immense importance. As a rule the younger the syphilis, the more marked is the response to treatment. True syphilitic aneurysm is a progressive affair and does not show the marked improvement under treatment that the clinician so often experiences in aortitis. Although the subjective improvement under proper treatment is often marked, and considerable evidence is accumulating to show that the progressive nature of this process can often be inhibited by judicious treatment.

Specific medication in cardiovascular syphilis demands the utmost caution. The administration of potassium iodid and mercury are rarely followed by untoward effects. Neosalvarsan, while powerful and efficient as a therapeutic weapon, is at times a two-edged sword. Occasionally the clinician is confronted with a cardiovascular syphilitic generally advanced in years, who, following the administration of neosalvarsan, experiences

an augmentation of his symptoms, which are unfortunately markedly intensified and often progress to a rapid and fatal termination. The explanations advanced to account for this clinical fact are numerous and varied. I believe this is a true Herxheimer reaction and that the biochemic reaction between the treponemata and the administered arsenical are unusual and abnormal, resulting not in the death of the invading treponemata, but in edema of the cells surrounding the invader and their rapid degeneration, with marked exacerbation of the clinical symptoms. The clinical facts in such cases support this contention. Fortunately, such disastrous results are comparatively rare, and in my experience have occurred only in those patients who are advanced in years and have long suffered from syphilitic involvement of their cardiovascular system. So constant has been this fact that I have abandoned the use of neosalvarsan in elderly cardiac patients who have suffered from syphilis for a long period of time.

The burden of the responsibility for the early recognition of cardiovascular syphilis falls not on the dermatologist or worker in syphilis, but on the general practitioner. I believe that if the clinician will examine every syphilitic for evidence of cardiovascular disease, and in the presence of any evidence, subjective or objective, utilize the x-ray and fluoroscope along with the Wassermann, the percentage of syphilitics with diagnosed cardiovascular syphilis will be increased. At this point it is well to recall that subjective evidence with a positive Wassermann precede the establishment of signs. Conversely, if the clinician will examine every cardiac case for clinical and laboratory evidence of syphilis the end-results will show a marked increase of cardiovascular disease attributed to syphilis. It is of extreme importance that cardiovascular syphilis be recognized as such, because untreated it is a progressive and often fatal malady. An accurate diagnosis and its subsequent treatment often arrest the degenerative process in the heart and great vessels and give to the patient many added years of comparative health and usefulness.

THE INDIVIDUAL RESPONSE TO SPECIFIC MEDICATION

THE problem of the mental trauma experienced by the individual who contracts syphilis is worthy of more than passing attention. This subjective reaction, associated as it is with the diagnosis of syphilis in the intelligent, may be apparently negligible, or in the individual of neurotic tendency may assume such proportion as to overshadow the underlying syphilis. Suicide is not unknown. Domestic complications are frequent, and the divorce court is a common sequence. The successful therapy of syphilis demands the physician's attention, that the mental reaction of the patient be considered as well as his symptomatology and seriology. Each individual case presents its outstanding features and complications, which to a degree may be allayed by a tactful handling of this often neglected detail in the management of the syphilitic. Encouragement and assurance that a symptom-free future may be reasonably expected by a patient who faithfully and persistently receives treatment is always productive of good, both on the mental attitude of the infected individual and his willingness to submit to prolonged future medication.

We will in the subsequent discussion confine our observation to the variations in response to specific therapy in syphilis of the acquired type in the adult.

Let us consider the possibilities and limitations of anti-syphilitic medication, and the clinical and laboratory evidence both pathologic and serologic concerning the end-result of therapy in constitutional syphilis. Certain it is, wide difference of opinion exists among the clinicians concerning what constitutes adequate treatment and subsequent clinical cure. When one considers the accumulated pathologic evidence now available in our literature, in which numerous investigators have demonstrated the *Treponema pallida* in the vital organs of syphilitics dead from intercurrent disease who contracted their syphilis twenty or thirty years previously, and during that period had been symptom free from direct manifestations

of their syphilis, cure must be interpreted as a balance between the host and the invading *Treponema pallida*. Clinically, when one sees a syphilitic who is symptom free and serologically negative following two or three years of mercury and neosalvarsan, relapse both serologically and clinically, the possibility of a cure in a given case becomes a complicated question. Syphilis and tuberculosis present numerous closely similar characteristics. The pathologic process may in both infections remain inactive through the subsequent life of the individual, a clinical cure, or at some subsequent time manifest themselves by renewed activity. In syphilis this renewed activity may involve any organ of the body or be manifest only by a positive serology. From the pathologic evidence one must believe that cure in constitutional syphilis is exactly equivalent to cure in tuberculosis, that the process is inactive, a clinical cure. Certain it is in syphilis that subsequent manifestations of activity, be they objective, subjective, or serologic, may in a vast majority of cases be eradicated by judicious antisyphilitic treatment. Occasionally developing activity may to a degree be predicted by the subjective manifestations and serologic evidence. Such an early activity responds rapidly to specific medication, although the serology may be unchanged.

We must regard the reactions of the body to the *Treponema pallida* which constitute the pathology of syphilis as a defensive measure. It is upon the success or defeat of these defensive reactions of the organism, indicated to a degree by the individual's response to treatment, that activity or clinical cure depends. Specific medication has a profound influence on the course of syphilis. It aids the defensive measures of the organism by the actual destruction of the etiologic invader. However, those *Treponema pallida* deeply embedded and fixed by connective tissue, defensive measures are not accessible to specific treatment, and these *Treponema pallida* may after years of apparent inactivity subsequently produce clinical manifestations of syphilis. We believe the clinical cure of syphilis to consist in keeping an individual symptom free throughout his life and, if possible, serologically negative. However, we should recall we

are treating first an individual whose Wassermann reaction is but a secondary consideration. This question of individual resistance to syphilis is so closely bound up with our results of therapy that it is difficult to unravel that which is due to therapy and that which is due to a relatively high immunity of an individual to syphilis. Often the advent of specific treatment decides the issue in favor of the host. The dispensary clinician is impressed by the aged derelict, often an alcoholic, who presents an extensive gumma over his lower tibia, who has contracted syphilis early in life, and over a period of thirty years has had inadequate treatment at irregular intervals. Careful physical examination of his vital organs show no gross manifestations of disease, while serologically he is positive to the superlative degree. Contrast this familiar figure to the young adult who is of neurotic tendencies undergoing severe mental strain, who has received two or three courses of antisyphilitic treatment in a period of five years, and subsequently develops a rapidly fatal paresis. In the presence of such facts which so frequently confront the clinician, one must conclude that the individual's degree of immunity profoundly influences the results obtained in our therapy.

It is not our wish to convey the impression that we are pessimists concerning the future of well-treated syphilitics. It is the exception who, years subsequent to his cure, suddenly becomes clinically and serologically active that proves in every case of syphilis some degree of infection escapes destruction at the hands of our specifics and fortunately in a majority of cases remains inactive throughout the life of the host. The subsequent activity in the minority of cases, with its disastrous chain of consequences, make the supervision of the syphilitic individual at stated intervals imperative and cause the thoughtful clinician to accept the term "cure" as a relative measure.

One must accept the conclusion that the individual's response to treatment varying over a wide degree, in accordance with the infected individual's relative immunity to syphilis, is frequently erroneously attributed to the efficiency of some particular form of antisyphilitic medication.

CLINIC OF DRS W W DUKE AND D D STOFER

CHRISTIAN CHURCH HOSPITAL

A SEVERE CASE OF ALLERGY DUE TO FISH GLUE

HYPERSENSITIVENESS to fish glue is a recognized, though rather unusual, cause of asthma and other allergic phenomena. The degree of hypersensitiveness against this allergin, studied especially by Cooke and his associates, may be extremely great—in fact, a case of death is on record caused by an intracutaneous test made with 0.01 c c of a very dilute solution of glue.

The following case observed recently by the writers had a reaction which nearly terminated fatally following the application of fish glue to a scratch on the skin, and this occurred in spite of the fact that the glue was almost immediately washed off.

The patient, a man of fifty-two, gave a negative family history of allergy so far as he knew.

He had himself been subject to asthma the year round for three years, most severe in the fall. He had been subject to hives, to angioneurotic edema, and frequent urination off and on since childhood. He had suffered a very severe illness (an acute reaction of allergy) several times after contact with glue. Two of these illnesses, which followed the licking of a postage stamp, were characterized by swelling of the tongue and lips, generalized redness of the skin, itching, hives, angioneurotic edema, and, finally, collapse which lasted about one hour. He had learned himself to keep away from glue. Upon one occasion he picked up a beer bottle with a wet lable and an attack followed similar to though less severe than the one described above. On another occasion he had put on a pair of shoes which had recently been repaired and within a few moments realized

that an attack was starting. He took off the shoes with great haste, but not soon enough to prevent a severe attack, associated with asthma, hives, angioneurotic edema of the feet, and generalized redness of the skin.

With this history we realized that the patient was extremely sensitive to glue and made our tests with the greatest of care. He was tested with all the common foods, pollens, animal hair, etc., and gave marked reactions to a great many of them, most marked to ovomucoid. He was later tested by the application of LePage glue to a scratch on the skin. An area of erythema soon appeared and the glue was washed off. Within a few moments a large hive appeared around the point at which the glue was applied, the patient turned red, began to cough, wheeze, and was laid down on a table. His blood-pressure dropped to practically nil and he said he felt as though he were dying. He had the most severe reaction which we have ever observed except one which occurred during a transfusion of blood due, we thought, to hypersensitiveness to milk, and we believe this attack would have terminated fatally had it not been for the speedy use of atropin sulphate, 1/150 grain, and several doses of adrenalin. After relief from this attack he had a recurrence in about one hour, which was again relieved with adrenalin. Following this he gradually recovered, and suffered apparently no further ill effect from the reaction.

Through the avoidance of egg and the removal of glue from his house (labels, books, stamps, etc.) he has been completely relieved of asthma.

The degree of hypersensitiveness which develops in certain individuals against foreign material is almost beyond belief, and it seems that glue to a sensitive patient ranks as one of the most intense poisons known to medical science.

ALLERGIC SHOCK AS RESULT OF BLOOD TRANSFUSION

BEFORE the discovery of iso-agglutinins the dangers of blood transfusion were great. In fact, while a medical student and intern, one of us observed 3 cases of death during, or a few hours after, a transfusion of blood. Inasmuch as transfusion was rarely performed at that time, these 3 cases represented a very high mortality ratio and were due, no doubt, to the use of incompatible donors. Since the method introduced by Moss for the grouping of donors according to their iso-agglutinins has been broadly used, reactions from blood transfusions have become much less common, and with the use of criteria as outlined by Lindemann in the performance of blood transfusion and in the selection of donors, severe reactions are rare.

The following case is reported as one of two examples observed by the writers of severe reaction during a blood transfusion, occurring in individuals whose blood had been tested with faultless technic so far as iso-agglutinins were concerned. Inasmuch as the reactions occurred immediately after the introduction of the first syringe of blood, the reaction could hardly be blamed upon anything except some incompatibility in the donor's blood which had not been discovered. This was thought to be hypersensitiveness on the part of the patient to a food which had been eaten by the donor, and is analogous, we believe, to the chronic allergy observed in infants, due to hypersensitiveness of the infant to some article of food eaten by the mother.

The patient was a woman of sixty-three, who had an outspoken case of pernicious anemia which had caused pallor noticed by the patient for a few months. She had, in addition to the anemia, a slight grade of hypertension and slight cardiac hypertrophy. She gave a history of having been subject to asthma at odd times in her life and that she was unable to take milk.

She was given a transfusion by the Lindemann method of 1000 c c of blood taken from a very large donor. At the end of this transfusion she was still moderately anemic. No ill effect was noticed. Fifteen minutes later when the second

donor was brought in she was talking brightly, had normal pulse, and apparently felt improved. The second donor was prepared and she was given 20 c c of blood. Before the second syringe of blood could be injected she said she felt a pain in her back, and within a moment she became unconscious—in fact, deeply comatose. Her pulse vanished, she stopped breathing, turned blue, and we thought she was dead. She was given three injections of adrenalin solution 1:1000 subcutaneously in 1 c c doses, and in about five minutes she began to breathe, move, her pulse returned, and within fifteen minutes she was again relatively normal. She has had no illness or untoward symptoms since this time, and her blood-count has gradually increased under the influence of the one transfusion which was given to 4,000,000.

Since the patient's serum with donor's corpuscles showed no agglutination after standing twelve hours, we felt sure that the reaction described could not be due to the presence of iso-agglutinins. There seemed to be only one reasonable explanation of the reaction, namely, hypersensitiveness on the part of the patient to milk. The patient was tested intracutaneously with all the common foods and gave a striking positive reaction only to milk. Each donor likewise was tested out to all the common foods, but gave negative tests to all of them. We felt, therefore, that the reaction was in all probability due to sensitiveness on the part of the patient to some constituent of the donor's blood—probably a digestive product of milk. Milk had been taken in considerable quantity by the second donor previous to the transfusion.

Hives have been observed to appear during or soon after transfusion of blood on numerous occasions. Symptoms resembling anaphylactic shock are also by no means unknown and have been attributed to agglutinins, hemolysins, etc. We have observed one other instance of reaction mildly resembling anaphylactic shock in a patient who was later proved sensitive to tomato and cabbage and for whom a donor had been used who had recently eaten tomato and cabbage. The bloods of patient and donor were thoroughly compatible so far as iso-

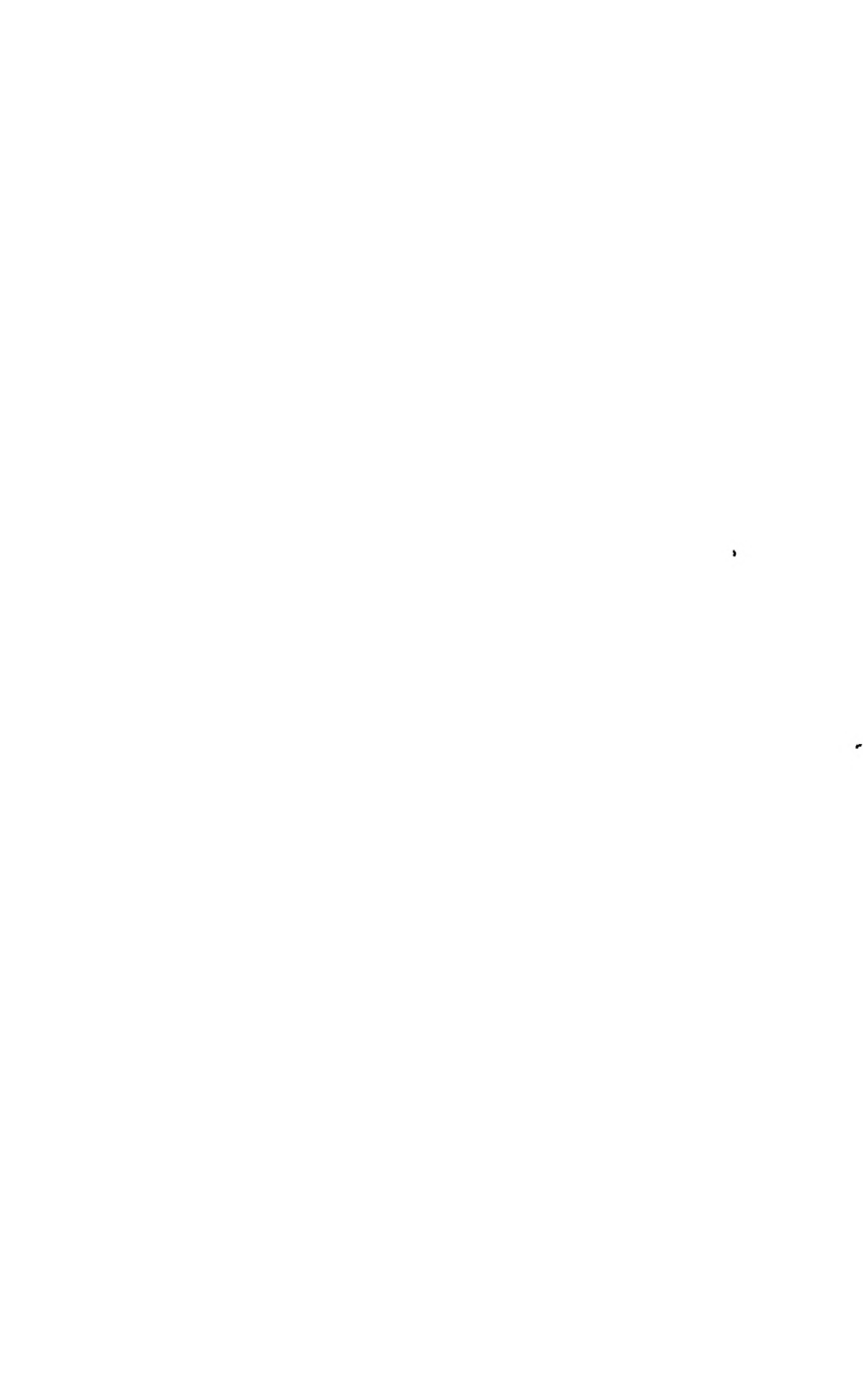
agglutinins were concerned, and we could discover no other adequate cause for the reaction

The testing of blood for compatibility is, we believe, not the whole story in the choice of donors for blood transfusion, and that in spite of the greatest care we believe that reactions will occasionally occur, even reactions of the greatest possible severity, due to hypersensitiveness on the part of the patient to some constituent of the donor's blood

For this reason we have modified our technic in the performance of blood transfusion and now inquire for a family and personal history of allergic symptoms in the patient before transfusion is started, and give a small amount of the donor's blood (1 or 2 c c) intravenously at the beginning of the transfusion. If this produces no reaction after an interval of several minutes, we feel that the blood is probably compatible and proceed with the transfusion. This precaution, I think, should reduce the few chances of mishap in the direct transfusion of blood where the donors have been carefully chosen

CONCLUSIONS

In the selection of donors for blood transfusion the testing of blood for compatibility so far as agglutinations are concerned should be carried out with the greatest care. In spite of this, however, the donor's blood may be incompatible and it is believed severe reactions may occur as a result of hypersensitiveness on the part of the patient to some constituent of the donor's blood. To avoid mishap, therefore, it is suggested that a history of allergic manifestations, such as hay-fever, asthma, and hives, be inquired for in the patient before transfusion is started and that a preliminary injection of a small amount of the donor's blood (1 or 2 c c) be made intravenously a few minutes before the transfusion is started. If this has no ill effect, the donor's blood would appear safe. This precaution, we feel sure, will eliminate some of the few accidents which happen during transfusion when the donor is compatible so far as iso-agglutinins are concerned and when the transfusion technic is flawless



CLINIC OF DR ROBERT C DAVIS

UNIVERSITY OF KANSAS MEDICAL SCHOOL

IMMUNIZATION AGAINST MEASLES WITH CONVALESCENT SERUM

THE important factor in the control of contagious disease is prevention. During the last four years we have used convalescent measles serum successfully as a preventive following exposure to measles.

In the study of contagious disease one is immediately impressed by the very contagiousness of measles. Different authors observing epidemics of measles place the contagiousness of measles at a very high percentage, varying from 95 to 99 per cent of all people who have never had measles and have been exposed. The death-rate from measles is not especially high, but from some of its complications the death-rate is very high. Take, for instance, some of the epidemics of bronchopneumonia in the Army Camps that followed the measles outbreak of 1917 and 1918, in which there was a very high mortality.

Due to the very contagious nature of the disease and the long period of incubation, *i. e.*, eleven to fourteen days it is very hard to stamp out the epidemic once an outbreak has started. Another fact which complicates the stamping out of an epidemic is that the prodromal symptoms which appear about the eleventh day resemble so closely those of an ordinary cold and coryza that the patient will not report to the medical officers.

It has been known for some time that scarlet fever may be immunized against, or if serum is given during the acute stage it very markedly modifies the course of the disease. We have

done some work both as to prevention and treatment, and have found it very satisfactory. Within the last few years the work of Richardson and Connor,¹ in which they report 6 children who were definitely exposed to measles, were protected from the disease by the use of immune serum. Eight others in which there was presumptive exposure did not develop after immunization. Three others who received the virus inoculation then received immune serum, and only one had an atypical rash. The work of Degkwitz,² assistant attending physician at the Munich University Children's Hospital, in his observation of 172 children who were given injection of measles convalescent serum, all of whom received the prophylactic injection between the second and sixth day, proved immune to the disease. McNeal,³ at Rochester, reports 16 children who were exposed to measles and who received the serum, 12 of whom remained free from measles and 4 of whom developed a mild form of the disease. Manchot and Reiche⁴ report in 155 children who received the serum after being exposed, only 11 developed the disease, and in all of whom it was exceptionally mild. Other workers have found very similar results. Nobecourt and Paraf⁵ report a series of 20 cases that did not develop the disease when the child is injected before the sixth day. Other workers have used horse-serum with what they think are satisfactory results. It is a question somewhat as to whether it is the immune bodies in the serum or the use of a foreign protein. However, in the work of Nobecourt and Paraf they used the injections of normal serum and horse-serum without any results. Many other workers both in this country and abroad have observed similar results.

Our work and interest was stimulated in this regard after reading the results of Richardson's and Connor's¹ work in the spring of 1919. We had just gone through a very severe measles epidemic in which there were a lot of complications in adults, as bronchopneumonia and otitis media and mastoiditis, and we adopted the idea of the use of convalescent serum along the line worked out by Richardson and Connor and Degkwitz.²

Our experience with the use of serum in the prevention of

measles has been, with the exception of a very few cases, in adults instead of children. The majority of the work has been done with male patients in the hospital from one of the largest Trade Schools of its kind in the world. The conditions are very similar to those in the Army Camps. There are new men coming into the school every day from every part of the country, and it is in this way we handle within the course of a year a large number of contagious cases.

In our first use of convalescent serum we tried it as a preventive after the patient had developed the prodromal signs and symptoms of measles, *i. e.*, the patient would enter the hospital with a temperature, signs of a cold, and Koplik's spots in the mouth. In all there were treated in this stage of infection 20 cases. As far as the use of the serum as a treatment, we were unable to notice few, if any results. However, we did notice in a few of the cases the eruption was delayed, in other words, the patient did not break out with a typical measles rash until three or perhaps four days after the appearance of Koplik's spots. Unlike in our cases of scarlet fever, who were treated with convalescent scarlet serum, we obtained no results other than a delay of the time of the eruption. The next step in the use of the serum was as Richardson and Connor, or as Degkwitz has done, the use of the serum as a prophylaxis.

In the series reported there are no cases in which there is a known previous infection of measles. The questionable cases are not included in this report. There are 4 cases not included in the series in which there is questionable measles early in life. At the present time we have immunized 52 patients against measles. There are only 2 cases in which any rash or signs of measles have developed following immunization. In no case included in the series is any case reported except those in which there was known to be direct exposure. In the greater majority of cases direct exposure took place either within the wards at the hospital in which a case would break out in a ward other than measles, or in a rooming-house in which these students live, and occasionally we could trace a case directly in the classroom.

Upon entrance to the school all students are given a medical card. Upon this card is asked the number of contagious diseases that the individual may have had. At the time a case appears within the rooming-houses or within the class-rooms the students who are exposed at the time are brought down to the doctor's office in the building and the nurse in charge questions each one as to whether they have had measles or not. In case they have not had measles, they are told that they may take the convalescent serum and thereby prevent the disease. It is not compulsory and is given only at the request of the student. In case the measles break out within the wards and there is direct exposure, the contacts are questioned as to whether they have had measles. In case they have not, they are given the convalescent serum. One instance this last year illustrates very forcibly the results of the use of convalescent serum. There were in one of the wards a number of patients with influenza. The first measles case of the year appeared in the school and broke out in this ward. All contacts were questioned, and those who denied having had measles were given the serum. One boy later developed a bronchopneumonia. He was put in a room with another bronchopneumonia patient following influenza, and was convalescing very satisfactorily when fourteen days later developed measles, and then developed a secondary bronchopneumonia and died. In the same room with him was a bronchopneumonia following influenza who had not had measles. He was immediately given convalescent serum, and on the fourteenth day developed an atypical rash which one would not have recognized unless he was watching for measles rash. He had no rise in temperature and no other signs or symptoms of measles and made an uneventful recovery. It is our feeling that had this first case known he had not had measles and had taken the convalescent serum, or the convalescent serum had been given to him, that he would never have had the measles, as our other case showed. The other case who had measles following the use of convalescent serum was in a mumps ward in which an outbreak of measles occurred. A student who had been admitted with mumps broke out on the fourth day with measles. All

the other contacts were immunized with serum. This contact who developed the measles was immunized with the same serum used on the other contacts, none of whom developed it. However, on his fourteenth day following exposure the typical rash of measles appeared, and the course of the disease did not seem to be influenced in any way by the use of the serum, as he had a very severe infection of measles. This occurred in the spring of 1922. At the time of writing this paper we have an epidemic of measles. We are giving immunizing doses of convalescent serum. Of patients whom we have observed for the full time of incubation following exposure and have had serum there has been only the one case as reported in the paper that has developed measles following exposure. However, it is not infrequent that many of the men who think they had measles in childhood develop them upon exposure.

The method for obtaining and giving convalescent serum is as follows. On the seventh to the tenth day after the patient has reached a normal temperature and in a patient who has had no complications, or in which there is no evidence of tuberculosis or syphilis, 500 c c of blood is taken from a vein in the arm by suction into an ordinary Ehrlenmeyer flask. This is allowed to stand at room temperature for twenty-four hours and then placed in the ice-box another twenty-four hours. Then the serum is pipeted off into 100-c c bottles and sufficient trikresol added to make the serum contain 0.2 of 1 per cent. Cultures are taken from all the bottles of serum to make sure that there is no contamination. The first two years during which we used this serum it was incubated to 56° F for thirty minutes. However, we have ceased the incubation. We have used serum as old as nine months which is kept continuously on ice and have not failed to get the usual good results. That is, this last fall we used serum which was obtained the previous spring, and in every case in which the serum was used no contact developed measles. As soon after the exposure as is possible the contact is given the first day 5 c c of convalescent serum. The two succeeding days 10 c c each day are given. In the use of the serum upon a large number of patients we have never seen any reaction.

and have never obtained any infection at the site of injection, nor have we observed any serum reaction as is frequently obtained with the use of horse-serum. The site of injection is very seldom complained of as being painful by the patient.

In the 20 cases in which we first used the serum as a treatment after the disease had developed, the only thing that we noticed was that it delayed the time of the appearance of the rash. At first we thought that it decreased the number of complications, but the epidemic in which we used it was not marked by a large number of complications, so therefore it is impossible to state as to whether there were any good results in the prevention of development of complications. Every epidemic of measles varies very much in the number of complications that develop. In one epidemic there will be a number of complications of bronchopneumonia, in the next epidemic one will have a large number of complications of otitis media and mastoiditis, so it is impossible to say whether or not there was any change in the complications observed by the convalescent serum as a treatment.

The difficulty in using convalescent serum in measles is that, for the most part, measles is a disease of childhood. We have been fortunate in having the large number of unexposed adults to treat who have lived in rural districts and who have never had measles. In the use of convalescent serum in the clinics in the larger cities it is very unusual to find an adult who has not been exposed and who has not had the measles. But these students come from the outlying districts some of whom have never had any of the contagious diseases, such as measles, mumps, and other contagion, and are, therefore, very fertile soil for contagion. For this reason we have been able to obtain as large amounts of convalescent serum as we desired to use, and therefore have not been handicapped by insufficient quantities. In orphan and foundling institutions and children's hospitals this type of work would be especially useful if the serum could be obtained, because of the known fact that measles epidemics in this type of institution have a high mortality. It is especially useful if a case of measles breaks out in some other

ward, as in scarlet fever or mumps, or in a room in which there is a pneumonia

Our complications, as otitis media and bronchopneumonia, are all isolated at the time of the development of the complications. The use of sheets between the patients, that is, of the cubicle, as was used in the army, has been used in the hospital for the last four years, but even with the observation of the strictest isolation occasionally a case will come into the ward and develop measles within a few days, having been exposed before admittance to the hospital and this is especially the type of case which spreads it all through the ward before it is recognized.

These cases are then inoculated with the convalescent serum, and it is this type of infection in which we have especially obtained our good results by keeping down the secondary infection from spreading through the entire ward. As an example of how this works, in St. Luke's Hospital last year I had a case of a young adult admitted to the ward whom I had never seen, and who the following morning was broken out with a typical measles rash. In this ward Dr. Dixon had 3 small children awaiting tonsillectomy who had never had measles. They were given the convalescent serum, one dose of 10 c c each, and escaped entirely developing the disease, and yet a nurse who entered the ward one time only and who never at any time cared for the measles patient developed measles. Another case was in a young girl who developed the disease. Her roommate was given convalescent serum. Both were sure of never having had the disease, and the roommate entirely escaped the infection.

In all we are reporting 52 cases that have had the convalescent serum following direct exposure to measles and who are sure they had never had measles. In the series only 2 cases developed the disease, the course of one of which was not influenced in the least, the other the only signs and symptoms of measles being an atypical rash which one would not recognize unless looking for the appearance of the disease, the temperature and the pulse not rising in the least. This case was just recovering from a very severe bronchopneumonia following in-

fluenza, and I feel that in this case he would not have been able to withstand the infection of measles superimposed upon his bronchopneumonia as evidenced by the boy who was in the same room with him and exposed him to the disease

Therefore one would recommend the use of convalescent serum following direct exposure to measles, especially when the individual is weakened by having had some previous infection from which he is just recovering. In children's hospitals, orphans' homes, or foundling institutions if upon the outbreak of an epidemic all contacts are immediately immunized within the first six days, as has been worked out by Degkwitz, Nobecourt and Paraf, and others, one would feel that a great deal of good could be done by immunizing all the contacts against the infection. It has been found by these and other workers that to obtain an immunity the contacts must be immunized the first six days following exposure, because after the seventh day the virus has been found to be within the blood-stream, and about the only good the immunization does is to delay the appearance of the infection or to modify it and make it an atypical measles infection.

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THE PROGNOSIS AND TREATMENT OF LOBAR PNEUMONIA

THERE is obviously a lot to be said concerning the prognosis and treatment of lobar pneumonia that one could not say in the short time allowed for the subject, but it will be possible to present a few points concerning pneumonia in general without going into the pathology or pathogenesis of the disease. Let us for a moment generalize upon a few points of prognostic importance because of its bearing upon treatment.

The conditions upon which one makes his prognosis are the age of patient, the temperature, the pulse, rate and character, the respiration, rate and character, the leukocyte count, the type of infecting organisms, and the area of lung tissue involved.

First, why does the patient develop pneumonia? Two conditions are necessary. One, exposure to the pathogenic organism, and the other and more important, the lowering of the individual's resistance.

As is well known, many persons are carriers of the organisms, yet never develop the disease, so another factor must be present, and, without doubt, the resistance of the patient is the more important factor.

There are a great many conditions whereby the resistance of the patient is lowered, among them other infections, as colds, sore throats, etc. Then there are those conditions so often described as exposure to inclement weather, wet feet and chilling of the body, and others of the same nature. Others, which I think play a more important part and which have not been stressed to such an extent, are worry, mental anxiety, and loss of sleep. In fact, in any infection if one gets plenty of good food and sufficient rest and sleep they are not so likely to develop the disease.

Then we are all familiar with another factor through our army experience—that of changing the ways of living. Let one go from one part of the country to another change his way of

eating, sleeping, exercise, etc., and there is a resulting lowering of resistance, whereby infectious diseases of the respiratory tract are more easily contracted

Now as to the age of the patient. Generally speaking, the increase of age about thirty-five years increases the mortality due to lobar pneumonia. Of course, one must bear in mind that there are no hard-and-fast rules in the prognosis of lobar pneumonia, and the more cases one sees, the more they are impressed by this fact. How often one sees a patient that according to the ordinary rules of pneumonia should not get well, but makes a recovery that is almost spectacular. Then again another, who should without any trouble make the usual recovery, gradually goes from bad to worse, and dies without any fight against a mild infection.

As an example, last year on the service at the Kansas City General Hospital, a patient entered during her second day of a Type III pneumococcus infection with a consolidation of the entire left lung. She was addicted to the use of alcohol and had been drinking rather large amounts of corn whisky. After a later involvement of the right lower lobe and a very stormy time she recovered. During the illness her pulse got very rapid and irregular. She became cyanosed and the respirations shallow and weak, all of which, as I will show later, are points of grave prognosis.

A temperature of 103° to 104° F seems to be the optimal temperature. We have been taught the higher the temperature, the more serious the prognosis. Our recent experience following the use of serum and glucose intravenously makes me rather doubt that there is any particularly serious nature of a high temperature, and another point in favor of a high temperature shows that the patient has some resistance to the infection.

The pulse is of more significance than the temperature. The pulse early in the disease is full and bounding in character. Later, as there is failure of the vasomotor system, the character of the pulse becomes weak.

A pulse-rate of 100 to 120 that is regular and of fairly good quality is of good prognostic value. As circulatory failure takes

place, there is either an increase in the pulse-rate with irregularity, or the pulse becomes weaker, more thready, and more compressible. Cyanosis usually appears about this stage. However, one may have cyanosis without heart failure, due to a respiratory distress.

The respiratory rate and character is of a great prognostic value. In general, the more rapid the respiration, the more serious the prognosis. The character of the respirations are very important. As the respirations become rapid and shallow, the patient is critically ill.

Another point in the prognosis is the cyanosis, which is of respiratory origin. It is due to an anoxemia and appears before circulatory failure. It is always of grave prognostic import when appearing in the disease.

The leukocyte count unless extremely high or extremely low has not a great deal of importance. The leukocyte count varies somewhat with the different types of infection. A count below 12,000 in pneumonia due to the Types I, II, or III pneumococcus or above 50,000 have a more serious prognostic value. A gradual falling leukocyte count usually means a lowering of the resistance of the patient. However, a rise does not necessarily mean an increased immunity, but usually an extension of the process or a complication as a beginning empyema.

According to the typing of the pneumococcus, as reported by Cole, the average mortality rate in hospital practice is about as follows:

	Per cent
Cases of Type I	25-30
Cases of Type II	25-30
Cases of Type III	45-50
Cases of Type IV	15-20

Thus from the above one sees the value of the typing from a prognostic standpoint.

The area involved is also of quite a bit of importance. One has observed cases in which with a very little involvement the patient is overwhelmed with an early toxemia and dies within a short time. However, usually the more involvement, the more

serious the disease. The severer types may start with only one lobe involved and gradually spread from lobe to lobe. This usually denotes a lessened resistance.

One serious involvement is the right upper lobe either alone or following other involvement. These cases are delirious, thrashing about in bed, hard to keep quiet or restrain. All of the cases of pneumococcal meningitis following pneumonia I have observed have followed a right upper lobe involvement. The mortality rate of right upper lobe involvement is very high.

There has been many articles in the literature concerning the observation of blood-pressure in lobar pneumonia. My experience with the blood-pressure has been that it is so varied that I am unable to give any serious consideration to it as a prognostic point. The rule of Gibson has not been borne out in our clinical experience. Very frequently I find a case in which the systolic blood-pressure in millimeters of mercury is constantly below the pulse-rate per minute, yet the patient recovers without any undue severity. The blood-pressure, when possible, should be taken every four to six hours. One point, however, I have observed which I think has some bearing on the outcome is that when the pulse pressure falls the outlook is not so good. This may be brought about by either a rise in diastolic pressure, the systolic remaining about the same, or a fall in systolic pressure, the diastolic remaining constant. I have observed a few cases in which there is a constant rise in systolic pressure, beginning at 110 to 120 and rising as high as 180. The diastolic remains low or even may fall. The majority of these cases have recovered.

Treatment—The treatment of lobar pneumonia might be divided into specific and symptomatic. The symptomatic treatment divided into means to conserve strength, relieve patient, and treatment of symptoms and complications.

Unfortunately, there is no specific treatment of lobar pneumonia. The serum even for Type I infections has been somewhat disappointing. Certain chemical agents have been tried by means of which a method to sterilize the blood-stream and destroy the infection in the lung was sought. As yet very little

has been attained. The chemicals tried have been optochin and quinin, both of which have caused destruction of nerve tissue when used in sufficient amount in experimental work.

There are several conditions which tend to conserve the strength of the patient.

Nursing—In securing a competent nurse one has accomplished a great deal toward the conservation of the strength of the patient. She must know what things are necessary for the patient's welfare and, above all, know what not to do. The nurse may overdo as well as the doctor overtreat. Make the patient comfortable, keep him quiet, free from worry, give plenty of water, and make him sleep. How many nurses we see in their overzealousness in trying to do for the patient, really do more harm than good, by tiring out the patient, causing him worry and anxiety.

Water—I am very positive that water is one of the best therapeutic agents that we have in the treatment of any acute infectious disease. The patient should be encouraged to drink large quantities. Of course, this can be overdone. One point to remember is that a sick patient will seldom ask for water. I like to see the patient take from 6 to 8 liters of fluids in twenty-four hours.

Fresh Air—By fresh air I do not necessarily mean real cold air. A good cool room with plenty of fresh air is very essential. It is not necessary that a breeze blow directly upon the patient. If he is having respiratory difficulty, cool fresh air acts as a respiratory stimulant. Patients with lobar pneumonia stand cold air better than those with influenzal pneumonia. In influenzal pneumonia I believe they are better with warm fresh air.

Applications to the Chest—These, with the exception of perhaps the pneumonia jacket, are mentioned merely to be condemned in the treatment of adults with pneumonia. I have never yet seen any good results from the application of a lot of sticky poultices, etc. to a patient's chest, and I am sure that harm has been done the patient by the moving, turning, and frequent application of such things to the chest.

When the patient has a pleurisy, which means an involvement of the visceral pleura, that side of the chest should be immobilized with either a jacket that can be strapped tightly or with adhesive tape. The objection to the adhesive strapping is that it hampers subsequent examinations.

Rest is the most important part of the treatment of lobar pneumonia. Not only is it important, but it is absolutely necessary. Other things being equal, a patient who gets plenty of rest during his acute pneumonia has many times a better chance of getting well than the patient who is restless, throwing himself about in bed, nervous, alarmed, raising himself up to cough and otherwise tiring himself out, and using strength that he should use in fighting his infection. Rest, besides being secured by the use of drugs, can be obtained by the reassuring of the patient by his physician, nurse, and by members of his family. Above all things, keep away from the patient those well-wishing friends who read all the death notices of all other patients dying of pneumonia. In fact, the least possible number of people that come in the sick room, the better. The nurse must obtain the confidence of the patient, as must the physician. Their every word and action must reassure the patient as to his welfare. The patient should not be examined too frequently. Examinations should be done for fluid in the pleural cavity and other complications. In turning from side to side the patient should not be allowed to turn himself in bed. The patient should be examined in the recumbent position, and only in very exceptional cases should he be examined sitting up in bed. He should be fed and given his fluids by the nurse. His strength should be conserved in every possible way.

Diet—The diet for the first few days should be a highly nutritious, easily digested one. Liquids, as egg-nogs and fruit juices, are especially desirable. Rest and quiet are much more important than the diet in conserving the strength of the patient.

Baths—A moderately warm sponge-bath quickly and quietly given once daily for cleansing the patient is essential. A short alcohol rub refreshes and strengthens the patient.

I have never seen any good results from cold baths to reduce the temperature in pneumonia. However, I have seen some very bad results due to the depressing effect on the respiration. Another bad result observed is the fits of coughing that are excited by the cold applications.

The temperature does not seem to have any deleterious effect and is of short duration as compared with typhoid, so it seems that little or no results are obtained by cold baths.

Drug Therapy—The drug therapy of pneumonia is very limited. The essential point to be kept in mind in the treatment is to help the patient along until he is able to develop his antibodies, and by his own resistance overcome the disease.

I have mentioned before that the treatment of pneumonia may be divided into "three plenties"—plenty of rest, fresh air and water.

I think the most important therapeutic rule in pneumonia is to not overtreat the patient. Drugs, until some specific has been discovered, are given for definite indications—for pain, restlessness, distressing cough, heart failure, and other symptoms as they arise. While on the subject, I wish to condemn any drugs which are not given for some reason. In our treatment of other diseases for which there is no specific, we have certain rules which we follow, chiefly certain drugs for certain symptoms. This is apparently not so in pneumonia.

How frequently we see patients treated with a whole list of drugs without the doctor having any explanation for their employment. It is not an unheard of proceeding for a patient over a period of several days to receive all or almost all of the following: three or four of the alkaline salts, aspirin, caffeine, quinin, phenacetin, hexamethylenamin, and various others, without there being any indication for their administration. I feel perfectly sure since our work of blood chemistry on pneumonias that harm has been done by the promiscuous use of alkalis in pneumonia. They have certain uses and when employed under those conditions seem to help. There seems to be but little acidosis in pneumonia. However, the so-called acidosis in pneumonia seems to be different from that in other conditions.

It occurs in those patients who are seen late in the disease and are dehydrated. It perhaps is due to a tissue destruction. The results by the administration of alkalies are perhaps not due to the alkalies so much as to the water administered.

In an uncomplicated case of pneumonia the only drugs I employ are digitalis and morphin. I use the tincture of digitalis and start the administration as soon as the diagnosis is made. I think I obtain better results than by waiting for the signs of heart failure and then administering the drug. At present I am using the tincture No. III of Parke Davis & Co. and am finding it very satisfactory. It seems to be less nauseating than the other tinctures we have employed. The method in which we employ it is to give it early and get sufficient into the patient so the heart is very easily digitalized thereafter.

* For example, in a patient weighing 150 pounds, we give 6 drams, giving 1 dram every four hours until the six doses are taken. Then after this using it in smaller doses as indicated.

Morphin is administered as necessary for pain, distressing cough, restlessness, sleeplessness, and rest. I have used morphin for all these indications for the past four years and I am convinced that it is the best drug in our armamentarium for the routine treatment of pneumonia. However, the same if not more care in its administration must be observed as is usual in any condition for which one prescribes morphin. I prefer to give small doses and repeat more frequently. By small doses I mean $\frac{1}{2}$ to $\frac{1}{8}$ grain.

Occasionally for restlessness and sleeplessness without pain I use veronal.

I employ, of course, certain other drugs for the symptoms as they arise, but the ordinary case of uncomplicated pneumonia as I see it in adults is treated with the two drugs as described above. Two years ago I tried the intravenous foreign protein in a series of 20 pneumonias, but my results were not any better than 20 treated in the usual way at the same time.

I think the so-called remarkable results obtained in any series of pneumonias are due to the low virulence of the infecting organism. The only way one can feel that his results are

accurate is to treat a series by the usual method at the same time he is carrying out his experimentation. Then if his mortality rate is much less his method of treatment is probably an improvement over our older methods.

Complications—Now, as to the complications usually encountered, perhaps the most frequent complication is fluid in the chest and empyema. I am unable to discuss the treatment of this condition at this time except to say I have obtained some very satisfactory results by the employment of gentian violet in early empyema. These cases must be watched carefully and the fluid aspirated without producing any pneumothorax. I have the impression that the use of serum and alkalies increases the number of empyema cases. However, I am at present unable to verify that opinion.

Delirium—In the cases of delirium one usually finds an involvement of the right upper lobe. I have for the past two years administered hexamethylenamin intravenously and feel that I have obtained better results than previously. At present I have not treated enough cases to reach a definite conclusion.

I do not use any drug to reduce the temperature, as the high temperature itself does not seem to have a bad effect.

Occasionally if one sees a pneumonia before the stage of consolidation and the patient is given a profuse sweat the disease seems to be abortive in type.

As to cathartics in pneumonia I use them only early in the disease, and then only once, the bowels being moved by an enema the succeeding days. If the patient has a well-developed pneumonia and is quite sick, no cathartic is given. The reason for this is the dehydration, weakening, and tiring out of the patient.

I have used glucose intravenously and have seen some very good results from its employment, but am not an enthusiast concerning it.

Strychnin and caffeine give good results as circulatory and respiratory stimulants but should not be used until indicated.

Camphor may have some use in pneumonia, but I have tried it rather thoroughly in both small and large doses, and am still

in doubt as to its beneficial results I have tried it in large doses in beginning pneumonia in an effort to abort the attack, but have not seen any appreciable results when used in this way

The use of alcohol in pneumonia I reserve to use only in those who are addicted to its use or to use in convalescence as a food

Now, in summing up the treatment in pneumonia, I emphasize the importance of rest, water, and fresh air. Rest to be brought about by not overtreating the patient and no useless exertion or movement

In the drug treatment of pneumonia we must realize we have no specific for pneumonia and do not overtreat and overstimulate the patient

CLINIC OF DR. W. A. MYERS

ST. MARY'S HOSPITAL

BOTULISM—AN ISOLATED CASE—ANTITOXIN AND RECOVERY

BOTULISM in man is apparently so uncommon in the Missouri Valley that I feel justified in reporting the following case with clinical and laboratory evidence collected, leading to this rare diagnosis. According to Meyer and Duborsky,¹ a review of the literature at least since 1912 shows no case of botulism has been reported from either Kansas or Missouri. These authors have recently performed a monumental service in culturing soil samples from every state in the Union, and in reporting that *Bacillus botulinus* has been cultured from some sample of soil from every state, with the exception of five. According to their important and interesting researches, the soil of Missouri showed positive cultures in 44 per cent of 34 samples tested, while Kansas soil was positive in 66 per cent of 30 samples. It would seem, therefore, that there is ample opportunity in either of these two states for botulinus infection of either man or animal. I am advised by the well informed that botulism in animals and poultry is not uncommon in this vicinity. However, the scarcity of the reports of the condition in man leads me to submit this case because of its being isolated and because of its occurring in a geographic area unsuspected by the majority of the profession of harboring the organism.

Case Report.—F. B., widow, aged fifty-four, lived alone, and frequently ate cold lunches. Three weeks before the onset of the illness she bought some unlabeled home-made mustard salad dressing from an unknown peddler. One week before she ate "a very little" of the dressing, with no ill effects. On

Saturday morning, November 4, 1922, she worked hard all morning, and at her noon lunch ate "about a half-teacupful" No one else tasted the food. She says that within "one-half to one hour" she began to feel queer, soon became nauseated, vomited frequently, had to lie down, and throughout the afternoon she could do but little work because of the vomiting and subsequent weakness. Toward midnight, or about twelve hours after the food ingestion, she complained of so much dimness of vision, dizziness, weakness, palpitation, and smothering spells that she had her family physician called, Dr. Frederick Campbell. He found her in a profuse cold, clammy sweat, with a rapid, irregular pulse, and gave her an emergency treatment of 1/200 grain of strophanthin intravenously. He saw her again next morning, and since she was so depressed, and since the case was obviously a medical one, he referred the case to me, with the excellent suggestion that it seemed to him a food poisoning, possibly a botulism. On my service at St. Mary's Hospital the following additional history and physical examination were recorded:

Patient says at about daybreak she began to see double, everything danced before her eyes, especially if she moved, she had precordial distress, with palpitation of her heart, was prostrated, and feared paralysis of the left arm and leg.

Some time toward morning she said she began to lose her voice, her throat seemed cramped, and she could swallow with difficulty. Dyspnea and "strangling spells," as she termed them, were so severe she feared she might smother to death. She had voided no urine nor had a bowel movement since the ingestion of her meal twenty-four hours before. She says there was no pain at any time.

Past and Family History—Has had perfect health except for measles and a light attack of rheumatism as a child. She has been married to a United States soldier, by whom there were two pregnancies, both ending in miscarriages. Her husband died four years ago from some illness the exact cause of which she denied knowledge, but said that in his last illness a spinal puncture was done, and following this by a short interval there

was a "paralysis of both legs" and death one year afterward. Father and mother died at eighty-three and eighty-two respectively—4 brothers and 3 sisters are living and well.

Physical Examination—At 11 30 Sunday morning the patient, a short, rather heavy, nervous woman, entered the hospital from an ambulance. Mentality was clear and the expression was rather of anxiety than of pain. There was no paralysis of any voluntary muscles apparently, but definite paresis of the occipitofrontalis, external rectus, and the entire left arm and leg. There was no blepharoptosis but a very marked nystagmus of the eyes, slow to the left, quick to the right. The pupils were unequal, the right dilated to 5 mm, the left measured about 2.5 mm, both reacted sluggishly to light and accommodation. There was a definite internal strabismus. The fundus was negative bilaterally. Tongue protruded without tremor usually in midline, slightly to the left at times. The muscles of the neck were so weak that she had to have her head supported, else it would fall by gravity to any direction. There was a rapid irregular heart, as mentioned above, but the chest was otherwise negative, as was the abdomen. On the left the knee kicks were exaggerated, a pseudo-ankle-clonus, and a very suggestive Babinski, on the right the knee kicks were present, even brisk, no clonus and no Babinski.

Other Findings—Temperature on entrance 97° F by axilla, pulse 84, irregular and intermittent, respirations recorded 24 and shallow. The W B C reported 23,500, with 84 per cent polymorphs. Blood-pressure 160/110. Catheterized specimen of urine recorded 500 cc, albumin positive, a few red cells and hyaline casts, otherwise negative. Blood-sugar 100 mg per cent, blood urea nitrogen 20 mg per cent. A blood Wassermann was taken and a spinal puncture desired but this was refused by the patient because she said her "husband was paralyzed by that."

DR MYERS Here is the history and the physical findings of a very sick woman. What is your diagnosis?

STUDENT It sounds like a cerebrospinal syphilis to me.

DR MYERS There are many things suggestive of it. The

patient may have had syphilis, certainly the unequal pupils and such a history would make one feel that lues would have to be ruled out. We shall speak of the Wassermann a little later—the fact was, the diagnosis in this case had to be made on the clinical findings, as the serologic tests could not be had for hours. I believe that a delay of twenty-four hours would have cost the patient her life, as some physicians despaired of her life as it was. Even if she had lues, this could not protect her against other acute illnesses. Furthermore, there is too much bulbar involvement, and too many cranial nerves involved, with too sudden an onset, we feel, to explain all these symptoms. What other suggestions?

STUDENT Encephalitis, I believe, often has a sudden onset, with diplopia, dizziness, nystagmus, pupillary changes, and with reflexes pointing to an upper motor neuron involvement.

DR MYERS Yes, or even with more of the symptoms mentioned in this case, such as asthenia, facial and pharyngeal nerve palsies, but in encephalitis cases we expect some lethargy, myoclonus, and fever. The onset is not, as a rule, so sudden, and I have never seen so much difficulty in breathing, swallowing, and speaking as was present here. What else would you have to rule out?

STUDENT Cerebral hemorrhage.

DR MYERS Yes, or localized edema of the brain. She had signs of acute nephritis—albumin, casts, and red blood-cells. We must be very skeptical about a hemorrhage causing so many widely separated lesions extending from the motor nerves of the eye to the face, throat, larynx, muscles of deglutition, and probably the phrenic and the spinal accessory, as well as the spinal motor tracts. It makes us think of multiple lesions.

STUDENT It might be polio-encephalitis.

DR MYERS Yes, you must remember that in this condition the onset may be very sudden, with paralysis as the first symptom. There is described a bulbospinal form which is extremely hard to rule out clinically here. Still there is typically more rigidity of the neck in polio-encephalitis. There is rarely nystag-

mus and fever is present You see there was no fever at any time in the history we read—it was rather subnormal

There are very few conditions that give leukocytosis with subnormal temperature and the picture shown in this history It is present in botulism In fact, with a few minor differences the history and physical findings fulfilled the classical picture of the discoverer of *Bacillus botulinus*, van Ermengem,² and if any of the syndromes mentioned by the student were present, it was not the exciting cause of the illness, and probably only a factor in obscuring the classical syndrome in its entirety, for instance, the bilateral dilated pupils frequently found in botulism, masked by a pre-existing syphilis causing unequal pupils Though I had never recognized a case of human botulism before, I have been extremely interested in the disease since hearing that the swine I used to see on the farm with paralyzed hindquarters or the cases of chickens with "limber neck" were probably animal botulism I have more recently been interested in some bacteriologic research, done in conjunction with Dr Breed, for *Bacillus botulinus* in encephalitis These studies have proved fruitless except to familiarize me with the value of the serum of *Bacillus botulinus* and to show me the picture in experimental animals In the case just presented we explained the vomiting following the meal by one-half to one hour, on the basis of action of an unusual amount of mustard, and that the actual symptoms of botulism began as would be expected about twelve hours after the meal, or, as she said, "at midnight." The symptoms arising within the first twenty-four hours after the ingestion could be in my mind explained by multiple disseminated vascular thrombosis a condition common in cases of botulism poisoning.³

The diagnosis and treatment of this case was made, therefore, on the clinical findings, the laboratory work, we feel, is highly confirmatory At 1 P M we gave 4000 units each of *Bacillus botulinus*, type A and B antitoxin, intramuscularly and repeated the same dosage at 8 P M There was no reaction from either injection This antitoxin was secured in this city from manufacturers, and at the same time their bacteriologist,

Dr Frank Breed, took samples of the salad dressing, and the three vegetables the patient said she had eaten, for bacteriologic cultures. Forty-eight hours later specimens of the patient's feces and urine were turned in for cultures, the reports of which, though valuable, were not available for two weeks after the inoculation of the media, but were then of the utmost import as corroborative evidence.

The history of the patient showed gradual but slow improvement. On entrance she could not swallow to exceed two small mouthfuls of fluid without complaining of choking, she had definite diplopia, and the bowels were parietic, retaining three enemata within thirty-six hours after entrance, one of these followed by 1 c c of pituitrin, without results. Rectal examination disclosed no evidence of impaction during this constipation. Within forty-eight hours she drank entire glasses of milk and cream, had diplopia only at times, and had a bowel movement following 1 ounce of castor oil. The pulse became much slower and much more regular, but the sinking spells and respiratory weakness did not markedly improve for many days. Following her discharge from St. Mary's Hospital she has been seen at intervals. Six weeks after onset many of the symptoms disappeared entirely. There remained some inequality of the pupils, but there was little or no dysphonia or dysphagia. Ten weeks after the onset she is back home able to walk with difficulty. Her left arm and leg are still weak.

The blood Wassermann report from the two laboratories on this case was negative. The spinal fluids, secured some days after onset, was reported negative to all tests, *i e*, Wassermann, cytology, globulin, and gold sol.

Dr Breed's report on the results of his work is, briefly, as follows. He cultured anaerobically in pork brain tubes samples from the various vegetables and the salad dressing eaten, and samples of the patient's urine and feces seventy-two hours after ingestion of the meal.

CHART OF TEST

Guinea pig No.	Date fed.	Amount fed	Culture made from	Results
429	11/22/22	0.5 c.c.	Tomato	Lived
430	11/22/22	0.5 c.c.	Lettuce	Lived
431	11/22/22	0.5 c.c.	Onion	Lived
432	11/22/22	0.5 c.c.	Salad dressing	Died—forty-four hours
433	11/22/22	0.5 c.c.	Urine	Lived
434	11/22/22	0.5 c.c.	Feces	Died—forty-three hours

His charts show that 0.5 c.c. of each of these six cultures were fed to as many guinea-pigs, all of which lived except the ones fed the cultures from the salad dressing and the feces of the patient, these dying in forty-four and forty-three hours respectively. This was rechecked (Chart 2), this time the culture from the salad dressing and the patient's feces were fed, each to 2 of 4 guinea-pigs, all of which showed typical signs of botulism poisoning, i.e., salivation and unsteady gait in thirty-two to thirty-four hours, and death from forty to forty-four hours.

CHART 2

RETEST OF SALAD DRESSING AND FECES CULTURES

Guinea-pig No.	Date fed.	Amount fed.	Culture made from	Results.
435	11/22/22	0.5 c.c.	Salad dressing	Salivation and unsteady gait—thirty-two hours Died—forty hours
436	11/22/22	0.5 c.c.	Salad dressing	Salivation and unsteady gait—thirty-two hours Died—forty-one hours
437	11/22/22	0.5 c.c.	Feces	Salivation and unsteady gait—thirty-four hours Died—forty-four hours
438	11/22/22	0.5 c.c.	Feces	Salivation and unsteady gait—thirty-four hours Died—forty-two hours

Following this the serologic typing test was used in which (Chart 3) 10 guinea-pigs were divided into two groups of 5 each—each of the first 5 were fed 0.5 c.c. of the salad dressing culture and each of the second 5, 0.5 c.c. of the feces culture. The first 2 of each group were given at the same time as the ingestion of the toxic culture a protective dosage of 25 units of

type A botulinus antitoxin. All of these pigs lived. The third and fourth of each group of 5 were given a protective dosage of 25 units of type B botulinus antitoxin. All of these died in thirty-six to forty-eight hours. The last of each group of 5 was given the toxic cultures, but no antitoxin—both of these died within forty-eight hours.

Dr. Breed's conclusions are briefly stated that the salad dressing eaten and the stool of the patient seventy-two hours after the food ingestion contains *Bacillus botulinus* spores or organisms identical in their toxicity and fatality to guinea-pigs, and that by typing tests the organism is *Bacillus botulinus* type A.

CHART 3

Guinea pig No	Date fed	Amount fed	Culture made from	Amount of antitoxin and types used	Results
439	11/25/22	0.5 c.c.	Salad dressing	25 units Type A	Lived
440	11/25/22	0.5 c.c.	Salad dressing	25 units Type A	Lived
441	11/25/22	0.5 c.c.	Salad dressing	25 units Type B	Died—forty eight hours
442	11/25/22	0.5 c.c.	Salad dressing	25 units Type B	Died—forty eight hours
443	11/25/22	0.5 c.c.	Salad dressing	None	Died—forty-eight hours
444	11/25/22	0.5 c.c.	Feces	25 units Type A	Lived
445	11/25/22	0.5 c.c.	Feces	25 units Type A	Lived
446	11/25/22	0.5 c.c.	Feces	25 units Type B	Died—thirty six hours
447	11/25/22	0.5 c.c.	Feces	25 units Type B	Died—forty eight hours
448	11/25/22	0.5 c.c.	Feces	None	Died—forty four hours

It would seem that the evidence here is logical and conclusive of a definite etiologic factor. *Botulinus* spores are not uncommon, especially in vegetables (though they seemed to be negative in these vegetables), but even when present there may be no toxic symptoms after their ingestion if there is not active growth and toxin production. It requires some medium suitable to

the growth of and toxin production from the organism to produce toxic symptoms in man. It would seem that the salad dressing fills all these requirements—it contained *Bacillus botulinus* organisms or spores, or both, and following ingestion it produced symptoms simulating human botulism. The same organisms fed to guinea-pigs produced animal botulism symptoms and death in suitable dosage, and specific antitoxin, types A or B (since it was polyvalent), in the human case, type A, in the case of the guinea-pigs, saved life. It has been shown experimentally that antitoxin given twenty-four hours after a forty-eight hour lethal dose will save life in guinea-pigs. We assume that it saved life in the human case, inasmuch as Burke,⁴ from his thorough studies on treatment, gives a prognosis as follows: A mortality of 70 per cent in American cases reported who have vomited, a mortality of 84 per cent in those attacked within twenty-four hours after ingestion of the food, and a mortality of 90 per cent in those first showing symptoms. All of these conditions apply to this case, and on this basis the life risk was extremely hazardous.

Another important evidence of this being a true case of botulism is the presence of toxic-producing *Bacillus botulinus* in the patient's feces. The presence of botulinus in human feces is apparently very rare except following true botulinus intoxication. The studies of Dubovsky and Meyer⁵ report negative cultures for botulinus in the feces of 80 people who had ingested vegetables bought in open market containing vegetables known by their cultures to be botulinus spore bearers. But in all of 4 of their positive cases of human botulism the feces cultures were positive, but in 2 of the 4 were found to be negative on the twenty-sixth and thirty-first day of the illness. From their very important and exceedingly accurate work it would seem that the intestinal tract of man has a tendency to self-disinfection when spores alone are ingested, but does this much less rapidly and effectively when toxins and spores or bacilli or all three are ingested in sufficient quantity to cause toxic symptoms. The ingestion of spores and bacilli without toxin does not seem to produce botulism unless in enormous dosage. We feel,

therefore, that the positive cultures of *Bacillus botulinus* Type A in both the food ingested and in the patient's feces seventy-two hours afterward, when associated with a botulism syndrome, is rather positive evidence of etiologic relation

Fortunately this patient did not die, so an autopsy report may not be here appended as further proof of etiology. Unfortunately, however, recent evidence would indicate that neither gross nor microscopic picture of this new and rather unusual lesion is above question. Instance the case reported by Geiger⁶ and by Dickson,⁷ in which autopsy findings by an authority in the pathology of this very disease justified a diagnosis of encephalitis, while cultures of the same brain, by an equally capable bacteriologist, also an authority on this disease, were positive to *Bacillus botulinus*. If thrombosis, described by Ophuls, were actually pathognomonic of botulism, and if perivascular infiltration were found only in encephalitis, the differentiation would be final at autopsy. Up to date, however, the history, physical examination, bacteriology and serology of botulinus intoxications are, we believe, safe etiologic criteria.

Conclusion —1 A case of botulinus poisoning from mustard salad dressing is here reported, so far as I can find, the first isolated from this medium.

2 It is of especial interest in that it was diagnosed clinically, though single and an isolated case—quite apart from so-called "outbreaks." Laboratory work confirmed the diagnosis.

3 It is found in the heart of Kansas City, the center of a wide section of America as yet not contributing any cases of human botulism to the literature.

4 Though a severe case of poisoning, with vomiting, early onset, and bad prognosis, the use of antitoxin within twenty-four hours after the food ingestion apparently saved life.

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CLINIC OF DR FRED J McEWEN

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BALANTIDIUM COLITIS

THE patient was admitted to the medical service of St Margaret's Hospital on February 3, 1923 complaining of diarrhea, severe cramp-like pains in the abdomen, and general weakness. He was forty-five years old. His illness began with a dysentery in 1898 while he was a soldier in the Spanish-American War stationed at Chickamauga, Georgia. In the following year he had almost recovered and was sent to the Philippines, where he was in the camp hospital for seventy-six days with severe dysentery, having from 12 to 20 stools a day. At first the stools were thin and watery in character, but later became semiformed and showed considerable blood and mucus. While in the hospital he lost 40 pounds in weight. Although not entirely well he returned to duty, but since that time had at irregular intervals acute exacerbations of dysentery with severe cramp-like pains largely in the upper abdomen, great weakness, and 10 to 20 stools a day. During one of these attacks in 1913 he was operated for appendicitis. In the past two years he has had several relapses, when he was unable to work and support his family. At present he has from 8 to 12 scanty stools daily. They are dark and contain considerable mucus.

His past and family histories are negative. He has never worked with or around hogs.

The physical examination revealed a man 70½ inches in height, weighing 130 pounds. He is fairly well developed, but poorly nourished. The skin is fairly dry and moderately tanned on the exposed surfaces. The eyes are sunken. The right

pupil is irregular and larger than the left. There is an indefinite history of injury of this eye in 1913. Vision is poor in the right eye, good in the left. Both pupils react to light and accommodation. The gums show a moderate pyorrhea. The teeth are dirty and some are carious. The tongue is coated in the center. There is no glandular enlargement. The chest is well developed and symmetric. Percussion and auscultation of the chest and heart are negative. The abdomen is flat and moves freely and equally on respiration. There is a slight, poorly defined general tenderness in abdomen. The liver dullness extends from the fourth rib to the costal border in the midclavicular line. The liver and spleen are not palpable. There is no muscular rigidity. The extremities, external genitalia, and neurologic examinations are negative. Proctoscopic examination revealed no ulceration in the rectum.

The laboratory findings are as follows. The blood-count showed 3,430,000 red blood-cells, hemoglobin 68 per cent (Dare), white blood-cell count 7000, differential count showed 60 per cent polymorphonuclear leukocytes, 13 per cent large mononuclears, 23 per cent small mononuclears, 4 per cent eosinophils, 1 per cent basophils, transitionals 2 per cent. There are no nucleated reds and no poikilocytosis. Platelets are abundant. The urine is negative.

Numerous stools were examined. They were fluid to semi-solid in consistency, dark in color, with scattered grayish-black patches. They contain some mucus and undigested food. The benzidin test for blood was strongly positive. The reaction of the stools was acid. No macroscopic blood was present at any time. Microscopically, they contained starch granules, fat, meat fibers, and numerous actively motile, oval-shaped, ciliated organisms corresponding in size, shape, and structure with the *Balantidium coli*. The anterior end was more pointed than the posterior end. A dozen or more were often found in a single field. No other parasites were seen. In the fresh warm stools the organisms were very active and could be seen drawing particles of food into the mouth or peristome by means of the cilia, and passing small particles from the rear. As the stool became

cold, motion ceased. The organisms were kept alive in the incubator for forty-eight hours in a solution of normal saline. The movement of these organisms was rather peculiar and irregular, sometimes being directly forward and at other times whirling or zigzag in character.

The treatment consisted of enemata of 15 per cent magnesium sulphate given twice a day for the first four days, one a day for four days, and then once every other day until the patient left the hospital, which was on the eleventh day after the treatment was given. At the same time the diet was changed to a non-fermentative type. Improvement was noted about the second day. On the seventh day no organisms were present in the stools and only a trace of blood. On leaving the hospital the patient still had 3 to 6 formed stools daily. At this time he felt quite well.

Two months after leaving the hospital he again returned feeling much better than he had before entering. During this period he had, however, a short relapse, but did not seek medical attention. The stools have remained 5 to 8 daily and were fluid to semifluid in character. No organisms were found and only a faint chemical test for blood.

Human *Balantidium coli* was first described by Malmsten in 1857 (quoted by Jollos and Bode). Since that time over 200 cases have been reported in the literature. The geographic location of these cases is wide-spread, Europe, Asia, Africa, North and South America, and the Philippine Islands being the usual location. The disease is not uncommon in the Baltic Provinces of Europe, and Bowman states that clinical material is fairly abundant in Manila and in the Philippine Islands. In the United States scattered cases have been reported from various parts.

Jollos describes the organism as one of the more common and important parasites of man, it has an oval shape and measures from 35 to 70 μ in length and from 25 to 50 μ in width. It is composed of two layers—an outer clear and homogeneous ectoplasm, covered with cilia which run in parallel rows from before backward and a darker granular entoplasm often con-

taining food particles and blood-cells. At the anterior end and to the left there is a wedge shaped mouth or peristome lined by cilia. There is no gullet. To the rear there is an anus from which the extrusion of particles may be seen. Near the center there is a kidney-shaped macronucleus and between its poles there is a small dark micronucleus. In the posterior portion of the ventral side there are two contracting vacuoles. These organisms fertilize by conjugation and divide by binary fission. Bode concludes that division by budding is most commonly seen in the human species.

Although about 25 per cent. of the cases reported have had contact with hogs, infection from hogs has not been definitely settled. Bode maintains that the human organism is not identical with that of the hog, and quotes Shegalow, who cited 54 men in St. Petersburg in 1899 who were "gut strippers" in a slaughter house. Forty per cent. of the hogs were infected, but none of the men became infected. On the other hand, many of the people in that neighborhood had infections with the human species of *Balantidium coli*. Furthermore, in Russia the same author states that there are very few cases, though the people live in the same building with hogs.

Klein in 1896 reported the organisms in the sewage of London and also in the city's drinking-water supply. This means of infection certainly is suggestive and in many cases it seems to be the most probable mode of infection.

Experimental production of the infections from the human cases to animals has been a failure in practically all cases. Bowman injected the organisms into the rectum of monkeys and colostomy openings without producing an infection. Bode failed to infect human beings with the hog organisms. The identity of the hog and the human species of *Balantidium coli* has not been definitely established.

The pathologic lesions appear to be largely limited to the large intestine (Bowman, Bell and Couret, and Jollos). The ulceration in the large intestine extends from the cecum to the rectum. The younger ulcers are shallow, with little thickening of the wall. The older ones tend to encircle the gut, are larger

at the base, which quite often is the muscularis, and have infiltrated underneath the edges of the mucosa, producing markedly overhanging edges in certain cases. The wall of the intestine is markedly thickened. Over the surface of the ulcers there is considerable necrotic material, mucus, and leukocytes. On microscopic examination the organisms are found in the walls of the ulcers, but never in the necrotic centers. They are also found in the lymphatics and mesenteric vessels. The wall surrounding the ulcer is heavily infiltrated with lymphocytes and plasma cells. The lesion shows a close resemblance with amebic infection.

Some authors question the pathogenicity of the organisms. However, the presence of the organisms deep in the walls of the ulcers and surrounded by a very definite inflammatory reaction along with the absence of any other etiologic factor affords evidence strongly in favor of an etiologic relationship between this organism and the lesions which are present in the intestines.

The organisms attack patients at all ages. De Buys reported a case in a child of five, although most of the cases are reported in adults.

Most cases begin with a mild diarrhea which gradually becomes more severe and then undergoes a remission, only to return at a later time, being more severe as the disease progresses. There is little or no fever. The patients complain of palpitation, flatulence, tenesmus, and cramp-like pains in the abdomen. Perforation of the intestine may take place. The symptoms may suddenly subside, only to return a month or so later. The stools are at first watery, then become semisolid in consistency. They are blood tinged or contain tarry appearing mucus. Frequently they number twenty or more daily.

Logan reported 4 cases with findings of pernicious anemia. The anemia improved rapidly with the improvement in the dysentery. This report is suggestive in connection with the statement made by Bode that many of the cases occurring along the Baltic region show a combined infection with both the *Balantidium coli* and the *Dibothriocephalus latus*. He quotes Voit who found *Dibothriocephalus latus* in 5 out of 12 cases.

of balantidium colitis Eosinophilia has been observed by some writers and not by others The infections are unusually very chronic and persistent, but become more severe as time goes on, and finally result in a fatal termination through general exhaustion of the patient

No standard treatment has been devised Enemata of tannic acid and acetic acid, boric acid, kerosene, silver salts, and weak iodine solutions have all been reported to be efficacious Thymol, emetin, distilled chenopodium, followed by catharsis, have been given by the mouth, with reported success, salvarsan intravenously was used in one case by Logan The experience of most authors is that the symptoms usually return sooner or later and in most cases the disease ends fatally

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CLINIC OF DR EDWARD T GIBSON

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CHRONIC IDIOPATHIC TETANY

WILLIAM R, aged thirteen, appeared at Mercy Hospital Out-patient Department March 14, 1923, complaining that he had had a spell of unconsciousness and that his hair was falling out

Present Illness —Investigation of his history shows that he has not been well since he was nine years old. Some of his symptoms and signs have been continuous throughout the four years, and others have been present only during the cold weather. With the exception of these seasonal variations his condition has grown neither worse nor better.

The continuous signs have been

- 1 Marked pallor of the face
- 2 A mild diarrhea, with two or three loose bowel movements daily
- 3 Diminished activity, which is noticeable especially at play
- 4 Awkwardness in all movements

The manifestations which have been confined to winter and early spring all began about four years ago, with the exception of the unconscious spells.

1 Attacks of dyspnea. These often follow running or excitement, but also come on without apparent cause and sometimes waken him from sleep. They last three or four minutes. His breathing is loud enough to be heard in the next room, and when the attacks come on at night they waken the family. There is a wheezy, whistling noise in the chest, and the boy complains that he feels as if he is suffocating.

2 Rigidity of arms and legs These attacks come on while in the bath, at stool, often without any apparent cause, and sometimes waken him from sleep They last from a few minutes to several hours They begin with tingling in hands and feet, which is gradually transformed into pain severe enough to make him cry The stiffness increases gradually for one or two minutes His arms and legs straighten out, toes pointed downward, wrists flexed, fingers straight, and thumb turned in He walks across the floor on his toes like a toe-dancer, trying to overcome the spasm, and presses the palms of his hands together in an effort to straighten them

3 Falling out of hair In the last four years the hair of his head has fallen out and been restored three times Each time it became dry and coarse and then became loose It could be pulled out by running the fingers through it After a few weeks it began to grow in again, the new hair being fine and soft About March 1, 1923 it began to fall out, and at present is beginning to grow in again

4 Unconscious spells In the winter of 1920 he had a convulsion with unconsciousness, and in the following month had three more In February, 1923 he had a fifth convulsion The attacks, as described by his mother, have all been similar He raised up in bed to a sitting posture, turned his head slowly to the right, and flexed his arms and legs strongly He "held his breath" for a short time and then breathed loudly There was a slight jerking of the limbs, but no tongue-biting or bed-wetting He was entirely unconscious during the attacks, and slept deeply for several hours afterward

Past History —The patient's mother nursed the next older child two months after she became pregnant with the patient, and had morning sickness throughout, but was not as sick as with her other children The patient was born at term, without instruments, and weighed 10 pounds at birth He was the largest of the family He cried at once, breathed easily, nursed properly, and gained weight normally First teeth erupted at ten months (dentition in all the children of the family at this age), he sat alone at seven months, walked at thirteen months,

and began to talk at the "usual time" He had measles at seven years, chickenpox at eight, pneumonia at ten, and whooping-cough at eleven Tonsils and adenoids were removed at Mercy Hospital at the age of eleven He began school at six years and is now in the fourth grade He has always been somewhat dull in school



Fig 229 —Trophic change in hair tetany

Family History—Mother was twenty-four at patient's birth and father was twenty-eight There are 5 children in the family, William being the third oldest None have died, nor has the mother miscarried The other children are well and have

had no trouble similar to William's The mother and one sister were dull in school

Physical Examination —Patient is undersized and poorly nourished, with dry coarse skin There is a general pallor, but the



Fig 230 —Tetanic spasm of hands

mucous membranes and conjunctiva have a good color The most prominent feature of his appearance is the scalp (Fig 229) The hairs are very scarce, but distributed equally They pull

out very easily There is no evidence of growth of new hair The scalp shows nothing pathologic There is no pubic or axillary hair The ordinary neurologic examination is negative Reflexes are rather inactive The following positive tests are pathognomonic

1 *Pool's Maneuver*—When the arms are held above the head so as to bring tension on the nerves of the axilla, after about two minutes the patient complains of cramps in the hand, which slowly flexes at the knuckles, the fingers remaining straight and the thumb turning in (Fig 230)

2 *Chvostek's Sign* (Phase 1)—When the region over the facial nerve in front of the ear is tapped lightly with a hammer there is a quick single contraction of the muscles at the ala of the nose and corner of the mouth

3 *Erb's Sign*—On testing the median nerve with the galvanic current contraction appeared at break with Kathode applied at 1.5 ma Normally contraction occurs at 5 ma at the lowest and usually only with much stronger current

Laboratory—Red blood-cells 3,920,000 per c mm, white cells, 5200, hemoglobin, 70 per cent Urine repeatedly negative Radiogram of head and chest showed nothing significant

Comment—The patient was observed in the hospital for a week On the first day he had a period of dyspnea with wheezing lasting about ten minutes His chest was full of whistling râles Attempts were made to induce tonic spasms by forced breathing and by exercises in the gymnasium, but without success He was given calcium lactate and parathyroid substance After leaving the hospital he had one more "asthmatic attack His hair ceased falling out and new hair has been growing Mechanical and electrical irritability of motor nerves has gradually diminished Response to tapping over the facial nerve trunk gradually disappeared, but it was noticed that long after Chvostek's sign became negative a very strong twitch could be obtained by tapping over the muscles themselves

Diagnosis—The increased mechanical and electrical irritability of the motor nerves and the characteristic tonic spasms are pathognomonic of tetany The distinction from tetany due

to removal of the parathyroid bodies and from such forms as infantile, gastro-intestinal, and the tetany of pregnancy is obvious. The age of the patient, the absence of obvious cause, and the chronicity, with seasonal exacerbation are characteristic of the group known as juvenile idiopathic tetany.

Etiology.—A number of interesting facts have been established, especially in recent years by metabolic research, but it is not yet possible to build out of these a satisfactory theory which will account for all cases. It has long been known that tetany follows removal of the parathyroid bodies, but, on the other hand, many cases of tetany which have come to autopsy have been associated with parathyroids histologically sound. Some cases yield promptly to the administration of calcium, while others do not.

Tisdall (Journ. Biolog. Chem., September, 1922) finds an increase of Na ions in tetany, and considers that all forms except the gastric depend upon a disturbed $\frac{\text{Na}}{\text{Ca}}$ ratio.

Gross and Underhill (Journ. Biolog. Chem., September, 1922) find a disturbed $\frac{\text{K}}{\text{Ca}}$ ratio.

Goldman (Journ. Amer. Med. Assoc., March 22, 1922) describes cases of tetany precipitated by forced respiration and thinks that a disturbed acid-base ratio is responsible.

Koch, of Detroit, and Paton and his associates, at Glasgow, have made some interesting observations upon the relation of guanidin to tetany. These workers have found that the injection of guanidin produces the symptoms of tetany and that in cases of both infantile and adult tetany there is an increased quantity of guanidin in the blood and urine. Barker (System of Endocrinology) suggests that the guanidin may be derived from arginin, a normal constituent of protein, if the ferment arginase, which breaks up arginin into ornithin and urea, were deficient. He suggests also that the formation of arginase may be a function of the parathyroids.

DISCUSSION

There are several features of interest in the case

1 In many light cases the manifestations of the disease are confined to the effects of increased excitability of the motor nerves. Here we have also increased irritability of the sensory nerves as shown especially by excessive sensitiveness to the galvanic current. There is also evidence of involvement of the autonomic nervous system—dermographism, facial pallor, diarrhea, and attacks of dyspnea. The patient was large and well nourished up to the age of nine, but has grown very little since.

2 Falling out of the hair has been mentioned several times in the literature (Bolten, 1917), but I have not encountered a case in which there was repeated disappearance with restoration.

3 The association of tetany and epileptic attacks are not unknown. Redlich in 1911 published a thorough study of the subject. He was able to collect 72 cases in which, as in the present case, the epileptic seizure accompanied or followed the tetany. Of them, 21 were in tetany following loss of the parathyroids, 17 in juvenile idiopathic cases, 5 in maternity cases, and the remainder in gastric and infantile tetany.

4 After Chvostek's sign could no longer be obtained in the usual manner, a very active twitch could be obtained by tapping near the muscle itself. This observation seems to fit in with the experiments of Paton and his associates on guanidin tetany in animals. They found that mechanical irritability of motor nerves was inhibited by the application of curare. They concluded, therefore, that the nerve ending is the seat of the greatest irritability in tetany.

THE PARALYSIS AGITANS SYNDROME IN NEUROSYPHILIS ¹

THE present tendency is to look upon paralysis agitans as a syndrome depending upon lesions of certain structures in the central nervous system. The disease processes which give rise to these lesions are of many different kinds, but two stand out with especial prominence, namely, atherosclerosis of the cerebral arteries and epidemic encephalitis. These two account for the great majority of cases seen at present. The syndrome is occasionally associated with a number of other diseases, among which is syphilis of the central nervous system. The following cases are of this kind.

CASE REPORTS

Case I —A B, male, aged fifty-five, complained of a tremor of the right arm. He states that the tremor began about two or three months ago and has steadily grown worse. It is intensified by worry or excitement and disappears during voluntary effort and while asleep. The right arm feels *queer*, but he cannot describe the sensation. In general, he feels very well, but is considerably annoyed by the tremor.

Past History —A B has had very little illness. In recent years there have been several attacks of sciatica, on both sides at different times. He frequently has fleeting pains over the arms and shoulders, and also more severe pains in the legs. These are sharp and momentary, but continue for three or four hours. They began about ten years ago. About twenty years ago he acquired gonorrhea, and at the same time had a little sore on the penis. He received no treatment for syphilis and no secondary signs appeared. He has had tonsillitis re-

¹From the Neuropsychiatric Clinic, Out patient Department, Kansas City General Hospital.

peatedly His teeth have been gone over recently and found to be in good condition Until recently he did executive work with a large manufacturing firm, but has now retired from business

Family History—Father is eighty years old and in good health, except for a senile tremor One son is said to have had specific epididymitis There is some tuberculosis in the family

Physical Examination—Well-nourished man of slight build There is a constant fine tremor of the right arm, with a "pill-rolling" movement of the fingers, rate about three to the second The arm is held stiff and the automatic movements associated with walking are absent in the right arm The face is somewhat mask-like During the examination a slight tremor of the left arm developed The pupils react well and are circular, but the right is larger than the left Eye-grounds are normal There is no definite or localized loss of power No sensory changes were demonstrated, but the patient says that stimuli feel different on the right arm Palpation of the muscles shows a distinct increase of rigidity of the right arm Reflexes biceps and triceps not obtained, supinators, present and equal, knee- and ankle-jerks were not obtained by any method of reinforcement Abdominal and cremasteric reflexes are present, and reaction on plantar stimulation is of the flexor type Cardiovascular and renal organs are normal Apparently normal psychically Clear spinal fluid under slightly increased pressure was obtained by lumbar puncture Examination showed

18 small lymphocytes per cubic millimeter

Globulin present (Ross-Jones)

Wassermann reaction 4 plus (Dr W K Trimble)

Gold solution formula 5544332100

Blood Wassermann 4 plus

In the next two months he received eight intravenous injections of neo-arsphenamin, with potassium iodid by mouth and mercury salicylate intramuscularly

At the end of this period the spinal fluid contained 12 cells per cubic millimeter, globulin plus, gold sol formula 1233210000

At this time the tremor of the arm was much improved, but rigidity was still present. The patient felt well, had very few pains, and did not return for further treatment.

After-course—A B's condition remained the same for a year. Then he became fussy and somewhat expansive. When the family was packing up to move to another house he insisted upon tying up parcels unnecessarily with paper and twine. Shortly afterward he began buying many useless articles, and talking about large business projects. He overdrew his bank account through foolish expenditures. He was sent to a private sanitarium and finally committed to a State Hospital.

Case II—C D, white male aged forty-two, came to the General Hospital Out-patient Department April 4, 1923, complaining that his arms were stiff and tremulous.

Present Illness—About two or three years ago D noticed that his arms were a little stiff. They became worse, gradually at first, more rapidly in the last year. He complains that they are so stiff that he can no longer follow his occupation as a teamster. Recently there have been at times a tremor of the hands and an excess of saliva, and the stiffness has extended over his entire body, rendering all his movements slow and difficult.

Past History—With the exception of infectious diseases in his childhood he has never been ill until four years ago. At that time he found a lodger dead in his house. This upset him so that he had a "nervous breakdown" and was in bed two months unable to walk. In February, 1923 he had influenza, but this did not affect the stiffness in his muscles at all. Five years ago he had gonorrhea and a sore on the penis, but describes nothing suggestive of secondary syphilis. He had a little treatment at the time. He was married sixteen years ago, and has 2 children, fifteen and thirteen. He was separated from his wife one year ago. At that time his wife and children were well.

He has never gone to school and cannot read and write.

He has used alcohol, but none in recent years. No drug habits. He has always been excitable and nervous.

Present Status—In general, he feels well, sleeps well, and has a good appetite. His stiffness and slowness of motion are annoying, but no worse. He feels strong enough to work, but cannot hold a job.

Physical Examination—He is a well-nourished man about forty. His face is expressionless, attitude stooped from shoulders, arms held close to body and flexed at elbows. Gait is slow and without associated movement of arms. Speech is monotonous. He responds to questions after a perceptible pause, but has no other defect in speech. His face is flushed and his lips usually moist with saliva, which frequently dribbles to his chin.

Pupils are unequal, left greater than right, and react very slightly to light, but more on accommodation to distance. Eye-grounds show mild optic neuritis. There is a slight tremor of head and both arms, frequency about three per second, disappearing on voluntary movement of the part. Muscles generally are in a state of hypertonus, with cog-wheel resistance to passive movements. Tendon reflexes could not be obtained, possibly on account of rigidity. No pathologic reflexes found. Sensibility to light touch and pin-prick everywhere present. No failure in co-ordination in upper or lower extremities.

Spinal puncture shows a clear fluid. Wassermann reaction 4 plus, globulin 1 plus, colloidal gold precipitation 2233210000.

THE SYNDROME

There are three striking characteristics of paralysis agitans—rigidity, tremor, and interference with normal automatic associated movements. The rigidity is distinguished from the spasticity of lesions of the motor cortex and its tracts by the absence of greatly increased reflexes, clonus, and the Babinski reaction. Cases of undoubted paralysis agitans in which some of these signs are present have also incidental lesions of the voluntary motor tracts. The most striking of the normal associated movements which occur automatically is the swinging of the arms in a manner suggestive of the quadruped gait. The

absence of this movement in paralysis agitans is an important element in the characteristic appearance. There are many other signs and symptoms involving secreting glands, vasomotor mechanisms, and the sensory system which are less constant.

CORPUS STRIATUM

Pathologic studies in cases of paralysis agitans have been confusing, because the lesions have not all been found in the same part of the brain. Thus we have cases carefully worked out in which the only lesion has been found in the thalamus (Leyden, 1864), the midbrain (Tinel, 1920), the substantia nigra (Souques and Tretiakoff, 1921), the internal capsule, in connection with apoplexy, but principally in various parts of the striate body. The most confusing pathologic reports are those in the classical type of Parkinson's disease accompanied by sclerosis of the cerebral arteries. Although there is always some lesion of the regions mentioned above, there are also so many other areas of softening that examinations of the brain have no value for localizing the essential defect.

I think we can remove some of the confusion if we think of nerve tracts and reflex arcs as the essential nervous mechanism and discard entirely the notion of nerve centers as the origin of nervous impulses. Modern neurology has shown clearly that every nerve impulse originates in a receiving apparatus and terminates at a muscle cell or gland cell, and that the cell body or the nerve center has mainly a nutritive function.

The practical point is that what we have to seek is not so much damage to any particular collection of nerve-cells as interference with the nerve tract leading to and from the center, as well as with the center itself.

Pathologic evidence points toward interference with nerve tracts passing through the striate body as the essential factor in paralysis agitans. The tract may be affected in the thalamus, in the striate body, or in the midbrain, especially in the substantia nigra and the red nucleus. Lesions may, of course, be not directly on this tract, but may affect it by extension peripherally, as in the cases of hemorrhage in the internal capsule.

FUNCTIONS OF THE STRIATE SYSTEM

The functions of the striate body and its tracts come out most clearly if one considers the phyletic history of these structures and their corresponding functions

In the fish there is no motor cortex and no pyramidal tract, the most anterior motor mechanism being the striate body. The movements of the fish have two striking properties (1) They are continuous and rhythmic and (2) they are associated from segment to segment so as to produce an undulatory effect. These movements are performed by the young fish without being learned, and are, therefore, automatic and depend upon a preformed nervous mechanism.

The lowest land-living vertebrates, the reptiles, have a much larger striate body than the fish, and one which differs in structure by the addition of a collection of cells of a different type. The striate body of the fish is composed of the large cells always associated with a motor function. The additional cells in the reptiles are small. The movements of the reptiles are very similar to those of fish, except that they are not continuous.

The additional small cells of the reptiles together with what motor cortex they possess are regarded as inhibiting the activity of the large cells of the corpus striatum.

In the higher vertebrates the striate body has the same elements, large cells and small cells, and also a greater development of the cerebral cortex.

The functions of the large cells of the striate body appear to be (1) the production of automatic associated movements, and (2) the maintenance of proper tone and stability in the muscles. The small cells seem to control the activity of the large cells.

If the large cells are destroyed, the result is loss of automatic associated movements, tremor due to faulty stabilization, and increased tone of the muscles, that is, the paralysis agitans syndrome. There are a number of other syndromes involving rigidity, tremor, chorea and athetosis which appear to depend upon destruction of the parts of the striate body involving the large and small cells in various proportions.

CONDITIONS WITH WHICH THE PARALYSIS AGITANS SYNDROME IS ASSOCIATED

It has been mentioned already that the great majority of cases of paralysis agitans are of the senile type, or follow epidemic encephalitis. Association with other diseases are surprisingly uncommon. In the older literature Fere (Twentieth Century Practice, 1897) mentions cases following influenza and tonsillitis. Lannois (quoted by Fere) has observed paralysis agitans with measles and with poisoning by charcoal fumes. Auerbach (Berlin Klin Woch, 1882) reports a case which developed after hemiplegia. Leyden (Arch f Path Anat. Berlin 1864, xxix, 202) described a case associated with tumor in the left thalamus. In the more recent literature one finds a case following concussion (Paulian, Bulletin et mem Soc Med d Hop Paris, 1922, 46, 645), one following typhoid fever (Hauser, Kiel 1903), and one or two associated with tabes dorsalis (Daddi Rev crit de clin med Firenze 1903, iv, 145, Placzek, quoted by Fere).

PARALYSIS AGITANS WITH NEUROSYPHILIS

The combination of neurosyphilis and paralysis agitans appears to be very uncommon. Loeper and Forestier (Progres Med, 1921, 36, 126) published a report of syphilitic lesions in the caudate nucleus. Lesions in the striate body are not uncommon *postmortem* findings in paresis. Christian (Amer Jour Med Sci, 1919 157, 271) reported autopsy findings in 162 cases of paresis. In 5 per cent there were small areas of softening in the lenticular nucleus of the striate body, and the following lesions were found occurring only once, softening of both caudate nuclei, softened area in the right caudate nucleus, old hemorrhage of right caudate nucleus, and thrombotic softening in the right lenticular nucleus. No clinical data are given in Christian's paper but one can readily understand how a syndrome due to lesions of the extrapyramidal motor system may easily occur in neurosyphilis.

The frequency of paralysis agitans following epidemic encephalitis throws emphasis upon the *locus* rather than upon the

disease process, or, in other words, leads to the supposition that even classical Parkinson's disease is merely a syndrome due to injury from any cause of certain structures in the central nervous system. From this point of view in the two patients presented the paralysis agitans is probably a manifestation of the neurosyphilis and not an independent disease coincident with it.

CLINIC OF DR A L SKOOG

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EPILEPSY

Case M N—This patient was admitted to the neurologic service of the Bell Memorial Hospital on December 11, 1922, and discharged March 3, 1923 White Female Single Age fourteen A student Her complaint was "cramps in the muscles"

Present Illness—The onset of the trouble dates back six years ago when the patient began to have "cramps" in the right leg accompanied by severe pain, but no loss of consciousness There were four such attacks during a period of a few days and each lasting over thirty seconds The frequency slowly decreased in the course of the first four months, during which time the patient was on bromid therapy All of the attacks during the first four years were diurnal During the second, third, and fourth years of the illness there were periods of from three to six months in which no seizures were observed About the pubescent period, which began two years ago, the seizures appeared with increasing frequency One year ago she was compelled to leave school on account of her physical condition The seizures have been sufficiently frequent and intense to oblige the patient to spend the most of her time in bed for some months The motor weakness and tendency to fall in the attack has had some bearing on this For several months prior to her entrance in this hospital the patient had had from four to five seizures during the day time and eight to fifteen at night Lately there has been a great deal of variation in the seizures At times only one extremity will be involved and at others two,

three, or four, and even the neck, head, and respiratory muscles may have participated. A shrill cry was heard frequently. Urinary and fecal incontinence was often noted. The cardiac and respiratory rate increased in the attacks. No frothing and no biting of the tongue was observed. Not much muscular soreness was complained of following the seizures. The mother maintains that loss of consciousness occurs only in a few of them. During the seizure period a tonic contraction in one extremity may be present, and clonic in another. All may pass through the tonic and then the clonic stages, with the following customary relaxation. At night the patient sleeps well between seizures. She is particularly liable to have an attack just as she drops off to sleep. They are aggravated during the menstrual period. An aura sometimes appears shortly preceding the attack, consisting of fulness and twitching of the toes. When localized the seizure is confined frequently to the right side.

Past History—Delivery was precipitate. There were no particular troubles during the first two years of life. She has had measles, scarlet fever, pertussis, and influenza, with no complications. When six years of age the patient fell from the back of a wagon, and was picked up in a state of unconsciousness which lasted a few minutes. No bleeding from the nose, ears, eyes, or mouth was recalled. She was always a strong, rugged, quiet, intelligent, industrious child with model habits, having a good disposition, and being a favorite with her school-mates. The menses began at twelve, with some irregularity, was scanty, but not painful.

Family History—One brother and one sister are living and well, none being dead. The father is said to be in good health, but had the reputation of being a moderate drinker without having been intoxicated. The mother is living and well. She had six miscarriages before the birth of this patient, and two following. Three self-induced abortions were admitted. Cancer, tuberculosis, metabolic disorders, endocrine disturbances, nervousness, or mental diseases among the relatives were denied. One grandmother was a mild morphin habitué, the habit having been acquired late in life to relieve rheumatism.

Examination —We have before us a well-nourished girl appearing to be about fifteen years of age. The chest and abdominal viscera seem to be normal. The tonsils show some evidence of chronic infection. The pulse and respiratory rate are about normal.

The head is well developed and of a normal size. No stigmata are in evidence. There is seen over the left forehead a scar, but beneath this we can palpate no bony depression. Skiagrams show no abnormalities. The sella turcica is normal. No evidence of ancient fractures are ascertainable now. In a study of the present mental status we can state that there is no dementia or imbecility. However, a general impression, from her facial appearance, conduct, and history, is gained that cerebration is slower than normal. Her conduct has been good at all times. There is no evidence of unusual irritability, periodic explosions, or violent moods.

Cranial Nerves —No abnormal function is seen for the first, second, or eighth pairs. The third, fourth, and sixth pairs present no great abnormalities. The pupils are large but regular. They are slightly unequal, left a little larger than the right. They react equally well to light and accommodation. The eye-ball movements are good. The eye-grounds show no radical changes. The disks are clearly outlined. No exudates are observed. Some hyperemia may be interpreted, possibly more on the left contrasted with the right. The motor and sensory fifth are normal. The seventh cranial nerves show no palsies. Facial movements, both voluntary and emotional, are good and about equal on the two sides. The ninth, tenth, eleventh and twelfth cranial nerves are normal.

Motor —In the spinal motor system we see no atrophies. During the first examination upon entering the hospital the patient was unable to stand unsupported. A considerable amount of weakness in the lower extremities, with possibly some inco-ordination was present. This was much more marked on the right side. Individual muscular tests involving the toe-, ankle-, knee- and hip-joints showed an impaired power both for flexion and extension. A similar condition was found in

the upper extremities. The spine seems to have a mild functional scoliosis. It could be bent voluntarily forward, backward, and either to right or left with full, normal movements.

Reflexes—The biceps and supinators were absent on the left, and present on the right. The right Achilles was present. The patellar was exaggerated, with a prepatellar. The right plantar was active. The deep reflexes in the left leg were sluggish, being obtained only by reinforcement. The Babinski and Oppenheim phenomena were negative on both sides. Tests for diadokokinesia revealed some defect, being much more marked in the right hand.

Sensation—Epicritic, protopathic, and deep sensations were normal everywhere.

All urinary and blood-counting analyses were normal. The clotting time of the blood varied from one-half to two and one-half minutes. A blood Wassermann was negative. A spinal fluid analysis showed a slight increase in pressure. There was a cell count of 4 lymphocytes per cubic millimeter. Globulin was absent. A negative gold sol was obtained. The Wassermann on the blood-serum and spinal fluid was negative. A Goetsch test gave negative findings.

A number of seizures have been observed by nurses and physicians. These throw no more light on the condition compared with descriptive reports at the time the patient entered the hospital. In many of the seizures there is no loss of consciousness. In some it is probably obtunded for a short period. The full recovery from the attacks is prompt.

Prior to the time of the operation the patient had been under luminal therapy, 1½ grains morning and evening. Parathyroid also was given during a part of this time. Under this method of treatment the seizures diminished both in intensity and number. The motor capacity likewise improved considerably. After being in the hospital a few weeks she was able gradually to be up more and more, and take progressively longer walks.

Operation—In view of the fact that the patient had been remaining more or less stationary for a few weeks, the seizures continuing, the patient clamoring for something to be done for

her relief, and there being very definite evidence of trouble in the left cortical region, it was decided to do an exploratory craniotomy on the left side to expose a large area of the left cerebral cortex in the neighborhood of the Rolandic region. The origin of the seizures in especially the right hand, arm, and leg and repeatedly continued in this region for many months the greater amount of impaired motility in the right arm and leg, and the increased deep reflexes drew our attention to the left Rolandic area as one in which we could expect to find some pathologic changes. The diagnosis of leptomeningeal trouble with possible cysts was made. We had no way of determining with any degree of certainty the possible amount of damage to the underlying cortex. With the clinical findings we were compelled to confess that we could not absolutely rule out some pathologic changes in the opposite pia-arachnoid and cerebral cortex. However, it was clearly indicated that a much greater amount of disturbance would be found on the left side.

Six weeks after leaving the hospital she was turned over to the surgical department for the left exploratory craniotomy, Dr Sudler operating. Nothing abnormal was found in the bone or dura. The leptomeninges were pathologic. There was an irregular amount of the sclerosis with here and there opalescent patches of varying sizes. There was a little increase in the amount of subarachnoidean fluid. The brain neither bulged nor retracted from the inner table. In palpating the different gyri in the prerolandic region I believed I could determine a difference of density in them, and in the various areas of the same gyrus. To a lesser degree this was true for the postrolandic area. I interpreted this as indicating an irregular sclerosis of the left cerebral cortex of the exposed area. Three small subarachnoidean cysts were found and evacuated. The pia-arachnoid was punctured at several points.

Shortly following the operation the patient developed a swelling of the face, much more marked on the left side, completely closing the eyelids. This seemed to be an edema without any inflammatory evidence. This practically subsided in

about one week. At no time was there any evidence of infection at the wound. There was a mild elevation in the temperature for about one week following the operation. The pulse-rate was correspondingly increased. For a couple of weeks the seizures continued at the rate of about one, two, or three per twenty-four hours, none being very severe, and usually generalized.

Now we are seeing the patient about four weeks following the operation. There is present a considerable improvement in the motor power. She walks about fairly well without support. There remains some evidence of motor weakness, especially more marked on the right side. The deep reflexes on the right side continue to remain a little brisker than the left. The patient admits feeling better, and has the appearance of being much more at ease mentally. Fewer seizures are observed or admitted by the patient who was always able to register herself every one. Again we have placed her on luminal therapy. It is the intention to continue this for a long period, the dosage to be arranged for.

DISCUSSION

I now wish to call your attention to and emphasize some of the salient facts and findings. It is quite evident that we are dealing with a case of epilepsy. Some of the more evident grave organic diseases involving the encephalon, such as brain tumor, multiple sclerosis, infantile cerebral palsies, neurosyphilis, organic brain states following encephalitis or meningitis, can be ruled out with a reasonable degree of security. Perhaps you might question whether we can eliminate hysteria with an equal degree of facility. The type of seizures, and the objective findings in the motor system, and the reflexes eliminate such a diagnosis. Perhaps some one may wish to use the term "hystero-epilepsy," admitting that there are evidences of a purely functional added to the organic trouble. I will acknowledge that it is possible to have a functional disorder superimposed upon a definite case of epilepsy or other organic brain disease. However, when such conditions exist we are dealing with a duplication of diseases. Personally there is not

much attraction to the term "hystero-epilepsy." Thus we will continue to discuss the case from the standpoint of a conclusive diagnosis of epilepsy.

I may point out that there is no history of similar or dissimilar heredity. Heredity is a potent factor in the etiology of epilepsy, but definitely more pronounced in the idiopathic type. Some authorities would prefer to use the term "essential" or "genuine epilepsy" in the place of idiopathic, to designate a type in which no etiology or anatomic changes can be demonstrated.

The onset occurred six years ago when she was eight years old, the patient having been robust in every way prior to that time. By far the major percentage of the cases of epilepsy begin between the ages of six and twenty. In fact some physicians would not accept the diagnosis of an epilepsy commencing after the age of twenty-five or thirty.

Originally her seizures were only of the diurnal type but in later years both diurnal and nocturnal were recorded. For many months from twelve to twenty seizures per twenty-four hours have been recorded. Fits may occur at night or during the daytime either in essential or in epileptic states where we have evidence of definite organic changes in the brain. It is only the smaller percentage of cases of epilepsy where the attacks are found alone in the daytime or alone during the night. I have demonstrated in a few cases where the seizures occurred only during the night that they could be reversed by having the patient remain awake and working at night and sleep in the daytime.

It is noteworthy that the tonic follows the clonic stage and this had been observed in any extremity where it alone was involved in the convulsive phenomenon. The variability in the involvement of various parts of the body is striking but with this there has been constantly a decidedly greater implication of the right side. I emphasize this as a strong indication of organic changes in the leptomeninges or an included pathologic state of the cerebral cortex in the region of the Rolandic area, and a greater degree of involvement of the left cerebrum.

Consciousness has undoubtedly been present throughout many seizures and lost in some stage of others. In many of the spells not even a slightly clouded conscious field or a momentary fleeting loss could be demonstrated, yet in the seizures without a deterioration of consciousness we clearly had other evidence of definite epileptic rather than a hysteric episode. A lost or greatly impaired consciousness is given as one of the striking or conclusive manifestations for making a definite diagnosis of epilepsy for either the grand mal or petit mal type. I have observed a few cases of certain grand mal epilepsy where there was no disturbance of the conscious field, the patient having been capable of detailing what transpired about and recalling all parts of a conversation during the seizure. Urinary and fecal incontinence occurring on a few occasions always strengthens materially the positive diagnosis of epilepsy. This state practically never occurs in hysteria. A somewhat indefinite aura has been recorded for some of the attacks.

It has been stated that there was no definite mental deterioration in our patient. However, there is most likely a slower cerebration. The cerebral responses varies a great deal in different individuals classed as normal. Thus we should be liberal in our interpretations. If the patient makes a complete recovery, all of the mental functions would be as rapid as formerly or as good as might be expected for her age. Perhaps you might say that her disposition and temperament does not indicate an epileptic status. The general practitioner is impressed with the irritability, unreasonableness, marked impulsiveness, and combativeness of the epileptic. I admit that such manifestations frequently occur among this group of disorders, both the petit mal and grand mal, but there are many where these undesirable traits are absent, where the patient does not cause much trouble and has a disposition not very different from that of the normal individual. The clean-cut organic or traumatic epileptic has, as a general rule, a more attractive disposition than the grand mal or petit mal.

Possibly the question might arise as to why we were justified in performing this operation on the brain. I might call

your attention particularly to the history of the type of seizures, involving especially the right leg and arm, the motor weakness, reflex state, and the occasional aura, all indicating a definite organic involvement of the cerebral cortex on the left side in the neighborhood of the Rolandic area. It was hard to determine whether this might have been one large leptomeningeal cyst or such a lesion in or near the cerebral cortex, or a diffuse sclerosis in this area. We could not rule out some involvement of the opposite side of the brain. We considered the possibility of several cysts in the leptomeninges overlying the left frontoparietal cortex. Where proper surgical technic is followed we feel that there is no more danger in performing an exploratory cranial operation through the frontal or parietal bones, using the osteoplastic flap method, than for a simple laparotomy.

Before concluding this clinic I wish to discuss briefly some of the types of epilepsy. Several different methods have been devised to separate the types of epilepsy. Here I might add that for many years I have been fully convinced that we could use advantageously the term "epilepsies" rather than epilepsy. We have to cover a group of disorders. That is especially true if we admit of the four grand types, namely, psychic petit mal, grand mal and focal, or Jacksonian, epilepsy. This division is based upon clinical manifestations. The psychic type is described in many of the text-books, but is not admitted by some authorities. Some insist that the psychic phenomena during the attack were possibly a manifestation of a petit mal inadequately observed. At the utmost an exceedingly small percentage of the cases could possibly be classified as psychic. The petit mal type is definitely more common. Petit mal may be found alone or passing into the grand mal at a later stage or the two types occurring at the same period in the patient. At times it is rather difficult to differentiate the petit mal from the grand mal seizures, even though some have been observed carefully. The grand mal includes by far the larger number, but there is a great deal of variation in the degree of involvement of consciousness, in the clonic movements, and the status immediately following the attack. True focal or Jacksonian

epilepsy comprises not more than 2 per cent of all cases. In a certain focal epilepsy, consciousness should be fully present during the entire attack. However, many cases begin as the Jacksonian type and later, possibly after one, two, or three years, gradually drift into the grand mal. Naturally the early period indicates judicious, vigorous treatment whether hygienic, medical, or surgical.

The general practitioner often has been impressed with the hopelessness regarding the treatment of epilepsy. Positively, the longer the epilepsy has endured the more difficult is the treatment with a consequent lowered recovery rate. Each seizure extends a slight invitation for a subsequent one. Thus in the institutions for the care of these patients that are usually seen at a later period, the recovery rate is small. In private practice it is considerably larger. The type offering the best prognosis is the focal, but many cases, even though you find such an attractive lesion as a simple cyst and where same has been successfully removed, do not result always in a recovery. Again several years must elapse before we can designate a case as a cure. Some neurologists and those dealing exclusively with the care and treatment of epilepsy use the two-, three-, or five-year period. I can recall one case of definite focal epilepsy centered in the facial area where I was called in consultation by one of the surgeons in Kansas City, an operation performed, and a cyst successfully evacuated, where the patient made an uninterrupted recovery and continued free from attacks for more than nine years while continuously at work, and recurred at the end of this period. A second operation in the same region permitted the removal of another cyst found among some thickened and adherent leptomeninges, which again promptly resulted in another cure. This patient now has been free from the attacks for another year.

The treatment might be divided into (1) hygienic, (2) medical, (3) surgical. Even though surgical intervention is used, most of these cases require additional hygienic and medical care for a long time. An even, regular life with care, and a properly selected diet is of much importance for many cases. All toxic

products whether exogenous or endogenous should be eliminated or reduced to a minimum

During the past half-century a large number of drugs have been advocated for the relief of this distressing group of maladies, but finally only a comparatively few need be considered for frequent use. Time prevents an extended consideration of this topic. However, I wish to say a few words on the relative merits for the bromids versus phenobarbital (luminal). Some would displace entirely the former with the latter. I am not convinced that such a policy is correct. There are times and cases where the bromids should be selected. Now I do use phenobarbital to a greater extent, compared with sodium bromid, in the general treatment of epilepsies. Phenobarbital, too, is not free from toxic or possible injurious results. Annoying or alarming toxic effects have been observed in many instances. The patients should be observed adequately during the course of the treatment. As a rule, I would advocate beginning with 1 to 1½ grains for an average adult, administered morning and evening. The increase in dosage should be governed judiciously.

The case before us illustrates one type of epilepsy which is difficult for a decision, as whether to advocate a cranial operation or not. I have cited another case of an entirely different type where the advice for surgical intervention was clearly indicated. The case, time, and area to be operated demand scientific, intelligent and judicious consideration.

MULTIPLE NEURITIS

Case M A—White female, age nineteen years, school-teacher, single She entered the Bell Memorial Hospital on September 7, 1922, with the complaint of inability to move the legs and pain in them

Present Illness—She informs us that during the latter part of April there was noted an impaired function in the forehead, that is, she could not wrinkle those parts as well as formerly Many facial movements had been lost, one side being no more involved than the other About the first of May, 1922 a tingling and numbness began simultaneously in the tips of all of her toes and fingers This soon left the fingers for a time, to return about September 7th These subjective phenomena have gradually progressed upward from the toes, until there is a definite loss of all forms of sensation An impairment of motor power was noted early, especially involving the lower extremities About the middle of August she went to bed because her lower extremities were no longer able to support the weight of the body The affection has always been more marked on the left side of the body, and involving the extensor groups to a greater degree than the flexor, causing a characteristic impairment of locomotion with a severe toe-drop No pain was noted until about the third week in August or about one week after she had been confined in bed The pain was sharp, continuous, and a little to the left of the coccyx, which seemed to be aggravated by movements of any kind It became progressively worse during the first two weeks in the hospital When entering the hospital she could not move her hips In a day or two after entering the hospital she complained of a rapidly increasing tingling and numbness beginning at the tips of all of her fingers, which gradually progressed After about two weeks she could only weakly flex her fingers and could not extend them at all, the left side being involved to a greater extent

The paralyzed muscles in both the upper and lower extremities were extremely hypersensitive, so severe as to cause a great deal of distress by the weight of the body on the bed. Even the bedclothing was extremely annoying. She complained of having been unusually drowsy and tired since the onset of the illness. About the time she became bed-ridden in August, Dr. C. O. Brown, who referred the patient, removed her tonsils. A prompt recovery from this operation was made.

Past History—She has always been a very active girl. No operation or any severe illness prior to the present trouble has been recorded. She had measles when a young child and influenzal pneumonia in 1918. Some time ago she had headaches which continued several years, especially after a long continuous reading in the evening. She wore glasses for about one year in 1918, which improved her vision. One year ago an oculist pronounced her vision good, and advised that no glasses be worn. For several years she had frequent attacks of tonsillitis until the offending organs were removed in August, 1922. There are no devitalized teeth. Two crowns and two fillings have been made, and one tooth was pulled in August, 1921 because of an abscess. She has never been constipated or had any particular gastro-intestinal disturbance. For a number of years only two meals per day were eaten. Her menses began at the age of fourteen, of five-day type and every twenty-one days. There is no history of any pelvic disturbance. She has never had any fainting spells, nor been considered nervous or excitable. Her habits have always been excellent and she has spent much time out of doors. The weight in August when she went to bed was 110 pounds.

Family History—Her mother died at an early age of abdominal tuberculosis. Her father died at the age of forty from "abscess of the liver." She had 1 brother and 1 sister living and well. Neural heredity is negative.

Physical Examination—We see a young woman presenting the evidence of having been fairly well nourished. Now there is a reduction of 35 pounds from the normal weight. Apparently there is no discomfort if she lies quietly in bed, and with the

lower extremities protected from the weight of the bedclothing by a wire frame. The skin over the chest and upper back is involved with an acne vulgaris. The scalp is clear. The remaining teeth apparently have been cared for properly. The gums are clean. The tongue is slightly coated. There is a foul breath. The tonsils apparently have been removed thoroughly. There is nothing remarkable in the lungs or cardiovascular system. The blood-pressure registers 118 systolic and 74 diastolic. There is no tenderness of the abdominal viscera. Some of the lower abdominal muscles give evidence of hypersensitiveness. When the patient attempted to lift the head off the pillow a considerable amount of weakness of the recti abdominales is evident. The patient is unable to support herself in a sitting posture, and if this is attempted pain is produced in the pelvic region. I believe that there is some weakness in the neck muscles. In the lower extremities we observe no possible voluntary movements at the toe-, ankle-, knee-, or hip-joints, either for a flexion or extension. In the upper extremities there is apparently a little weakness of the pectoral and shoulder group of muscles, probably a little more involving the deltoid. The biceps and triceps probably have about one-third normal power, a little weaker on the right side. The patient can grasp feebly, a little better with the left hand. There is no voluntary wrist extension. All of the forearm muscles are much weakened, extensor much more than the flexor group. The intrinsic muscles of the hand are extremely weak. The muscles which are weakest show the greatest amount of atrophy. Especially is this atrophy noticeable in the intrinsic muscles of both hands and in the forearm. Probably there is a greater amount of atrophy of the muscles of the leg. There is a total absence of all the deep reflexes for both the upper and the lower extremities. The abdominal reflexes are sluggish. When the upper extremities are used there is a little tremor which is due entirely to the weakness. No true ataxia can be demonstrated. Sensibility is impaired in the lower extremities, more in the distal parts. No true neural segments of peripheral nerve areas can be outlined. With this impaired epicritic sensibility which is present also in

the hand it is interesting to note that the deep muscle sense is extremely hyperesthetic, especially in the lower extremities. The plantar, Oppenheim, and Babinski tests give negative findings. Passive movements of the lower extremities produce a great deal of pain, somewhat diffused or referable to the muscles. The soles of the feet are insensitive to heat, cold, touch, or pain. The dorsum of the toes is slightly sensitive to painful stimuli.

In reviewing the laboratory analyses we find that the urine is negative in every way. The blood analysis has shown erythrocytes 3,984,000, hemoglobin 80 per cent, leukocytes 7000, with a differential count of about normal. The clotting time was three minutes. A lumbar puncture was done and the spinal fluid found clear, under slightly increased pressure, with a cell count of 1 lymphocyte, a slightly increased globulin, and a negative Wassermann and gold sol.

There has been during the past two weeks a slight elevation of temperature from time to time and a mild increase in the pulse and respiratory rate occasionally.

The patient has now been in the hospital two weeks. During the first week there was a definite increase in her trouble, particularly for the progression of the motor incapacity. At the end of the second week there was no improvement in the motor condition. The sensory condition has improved some. The patient is considerably more comfortable than at the time she arrived at the hospital. On a number of occasions I would enter the ward and find the patient crying. At times she could give a good reason for this emotional state and at others not.

There is no great amount of damage for the mental functions. However, there is a definite diminution of cerebration. Memory is slightly impaired. She remains perfectly orientated and gives relevant answers to all questions. In the emotional sphere we see more impairment. She is easily irritated and vexed. Much unnecessary crying is indulged in, which is a departure from her natural state.

Among the cranial nerves there are no severe palsies. Vision is fairly good. Examination of the eye-grounds reveals a feeble

cipping. The disks are not perfectly well outlined. There is some questionable pallor of the temporal side of the disks. The blood-vessels are clearly outlined. The pupils are large but equal, and respond to light and accommodation with probably some diminution of range. Hearing is normal. The senses of smell and taste are good. No paralysis of the fifth, ninth, tenth, eleventh or twelfth cranial nerves can be noticed. There is a definite weakness of the seventh cranial nerve probably a little more on the left than on the right. There is much tremor in the tongue which is protruded mesially and to a fair distance.

In the care and treatment of the patient covering the past two weeks much concern has been felt about the extreme sluggishness of the bowel functions. Enormous doses of cathartics have been required constantly to combat the constipation. The difficulty can be attributed to the impaired physiology of the intestinal tract conjointly with the paresis of the abdominal muscles. Also we must bear in mind that she is unable to take any exercise which might stimulate the function of defecation.

We have before us a patient evidently with an enormous impairment in the motor system and less in the sensory. The clinical syndrome is definitely one of some organic diseases of the nervous system. It is hardly necessary in a differential diagnosis to entertain any functional disorders. The involvement of the peripheral nerves is quite evident, and we do not hesitate for a moment in making the diagnosis of multiple neuritis with a greater amount of involvement of the lower extremities.

Continuing on the nervous system we might ask the question as to whether the spinal cord is involved or not. When analyzing both the subjective and the objective neural findings we are inclined to believe that the spinal cord is involved also. In other words we have a myelitis. This probably involves the lower motor neuron centers in the anterior horns relatively more than the lateral or posterior columns.

Again in our diagnostic considerations of the neuropathologic changes in this case we might ask questions relative to

the invasion of the brain. It is quite evident that both seventh cranial nerves are palsied. It is rather difficult to determine what portion is peripheral, or how much may be referred to histologic changes in the nuclei of the inferior neuron of the facial nerves in the lower pons. I believe that we have a definite implication of the central ganglia of the brain. This is indicated by the emotional disturbance. An involvement of frontal, parietal, and temporal lobes is not so clearly indicated. I believe that there is a little disturbance of cerebration which may be accounted for by mild pathologic changes in cortical nerve cells or association pathways.

The prognosis for this patient will be dependent upon several factors. In the first place, if there is not much damage to the brain or spinal cord the prognosis is decidedly better. In a case of multiple neuritis, strictly limited to the peripheral nerves, the outlook is fairly good for a complete recovery. However, in this patient I would give a somewhat guarded opinion in view of the fact that I consider that there is a definite involvement of the spinal cord. It is a well-known fact that that portion of the neuron in peripheral nerves can be restored even though severe palsies are present. This is not true for a myelitis where only milder types make a fair degree of recovery. Regeneration of destroyed neural pathways and nerve-cells in the spinal cord is impossible. For the prognosis we must also consider the etiology.

In this patient we have definitely eliminated any possibility of syphilis or tuberculosis. We know that a great many different causes for multiple neuritis have been described. They may be divided into four groups. (1) Traumatic. In this patient there is no history or evidence of trauma. Furthermore, such a universal involvement of peripheral neurons does not follow an injury. (2) Exogenous intoxications. We have no evidence or information of any organic or inorganic chemicals such as alcohol, arsenic, and various drugs that might have been used. (3) Endogenous intoxications are not so readily eliminated. There is no proof of diabetes, pernicious anemia, or other metabolic disease. We have no history of constipation

prior to the patient's illness. Possibly after once established her illness might have been aggravated by the constipation which had been of a severe degree. (4) Bacterial. The literature during the past few years contains much material by a number of different special authorities demonstrating neuritis, myelitis, and encephalitis resulting from infections of one kind and another. Our attention has been called particularly to distal focal infections. In this patient we can find nothing in the ears, nose, teeth, genitalia, or intestinal tract which would be a primary focal source for the neural illness. The same cannot be said for the throat. This patient gives a history of a number of attacks of "sore throat" and tonsillitis. There is also a history that her tonsils were successfully removed about one month ago. The question may arise, if we consider that her trouble was caused by tonsillar infection, why she did not begin to recover promptly following the removal of the tonsils. She progressively became worse for at least five weeks following the tonsillectomy. I believe it would be safe to answer this question by stating that the infection has become thoroughly lodged in the nervous system, particularly in the interstitial tissues of the peripheral nerves. Finally, I wish to emphasize the fact that the etiology in this case most likely dates back to the former tonsillar trouble, from whence came an attenuated pleomorphic streptococcus to invade the interstitial tissues of the many nerves.

The treatment as shown in the order chart has consisted of rest and a protection to the lower extremities by means of a wire frame. The position of the patient also is shifted frequently. This reduces undue pressure to a minimum. If the opportunity offers itself for a patient of this type I would recommend highly a water mattress. This, when filled with warm water, will be kept at a comfortable temperature by the heat emanating from the body of the patient. This gives an equalized pressure over a large percentage of the surface of the body. Alcohol rubs have been used, but must be given rather carefully to the lower extremities on account of the hypersensitive state. A few doses of chloral and codein hypodermic-

ally were used for extreme pains. Sodium salicylate in 20-grain doses, and sodium bicarbonate, 10 grains, have been given t i d. Aspirin or atophan might be substituted for the salicylates if the stomach revolts. A few doses of pyramidon, 7 to 10 grains, also have been given for the pain. While large doses of commonly known laxatives and cathartics have been given, yet we have been compelled to rely mostly upon soapsuds enemas to evacuate the lower intestinal tract. The question of electricity, massage, and mechanical therapy might be considered for this patient. At the present time there is too much acute involvement of the peripheral nerves and muscles to consider any such active treatment. The lady would suffer intensely under such treatment at the present time, and no gain would result. At a later stage in the course of the disease when all, or nearly all, of the active acute process has subsided, these treatments will be appreciated and recommended to the patient.

SUMMARY

Summarizing the leading clinical data and the interesting facts in the case before us, (1) I wish particularly to call your attention to the severe type of multiple neuritis, a moderate amount of myelitis, and a lesser encephalitis. (2) That in a patient with these combinations we must be guarded in our prognosis. (3) There is much to be considered in the treatment and general care of the patient, but therapeutic measures must be applied correctly at the proper stage of the disease. (4) The poor advice and treatment by irregular and incompetent men during the early stage of the disease before the family physician obtained control is to be regretted. The present serious state of the patient could have been prevented by earlier appropriate therapeutic measures.

CLINIC OF DR H R WAHL

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CARCINOMA OF THE BILIARY TRACT

Case I. Primary Carcinoma of the Gall-bladder—This old lady, aged seventy-five, complained of pain in the chest and abdomen beginning suddenly nine months ago. It was followed by increasing shortness of breath and swelling of the feet. Then the abdomen began to enlarge. She has had some dizzy spells and occasional vomiting attacks with some jaundice which, however, was never prominent. She had lost much weight and felt weak. This patient has had both syphilis and malaria. She was married, but has not had any children.

When admitted she appeared pale and anemic. Her breathing was labored. The skin had a pale yellow color, was dry, wrinkled, and loose. The liver was enlarged and very tender. The feet and legs were edematous. A large globular mass the size of an orange could be felt in the left nipple line at the level of the umbilicus. It moved with respiration. There was marked constipation. There was so much difficulty in getting a bowel movement that a partial obstruction in the colon was suspected. The stools appeared normal, but contained considerable blood which was not recognized macroscopically. The blood showed a red count of 2,500,000, hemoglobin of 23 per cent, and white count of 16,200. There was a \pm plus Wassermann reaction on the blood. Gastric analysis showed absence of free HCl and a total acidity of 18. A few days after entering the hospital she complained bitterly of the pain in the upper abdomen especially when her bowels had not moved. The patient gradually weakened, the abdominal pain and discomfort increased, the breathing became more labored. There were several smothering attacks followed by chills and moderate

fever. Involuntary bowel movements followed, and death occurred twenty-six days after admission.

The symptoms of this patient indicated an abdominal malignancy the source of which was in doubt. At first a carcinoma of the stomach with metastases to the liver was suspected, but with completely negative gastric findings, with persistent blood in the stools, and the obstinate constipation and abdominal flatulence the diagnosis was changed to a primary carcinoma of the colon with empyema of the gall-bladder.

At autopsy the main findings were as follows. The skin had a pale lemon yellow color. The feet were swollen and edematous. There were about 2000 c. c. of a bloody fluid in the peritoneal cavity. The liver was very much enlarged and had on its surface several large rounded soft tumor masses. It weighed 3640 grams. One of the tumor masses was about the size of an orange and hung down from the edge of the left lobe over the pyloric end of the stomach. It was soft and hemorrhagic and its lower surface ragged and bleeding. The right lobe was largely replaced by large rounded masses of soft, soggy, friable tumor nodules 1 to 7 cm. in diameter. There was such a mass of dense adhesions about the gall-bladder that it was not recognized at first. These adhesions matted the gall-bladder, the hepatic flexure of the colon, and the duodenum in one mass. Careful dissection showed that one of the larger masses of tumor tissue in the right lobe was the gall-bladder which was almost filled with friable tumor tissue and had a dense fibrous capsule and a ragged friable lumen continuous with a large perforation 4 cm. in diameter on the anterior surface of the duodenum. There was a smaller perforation 1 cm. in diameter into the hepatic flexure of the colon. Both these openings were matted down and separated from the peritoneal cavity by adhesions. The common bile and cystic ducts were dilated. The cystic duct entered and was lost in the soft tumor tissue. There were no tumor masses in any part of the gastrointestinal tract nor in the pancreas. The hepatic flexure, besides being the seat of the perforation, was bound down and kinked by adhesions, resulting in considerable stenosis of its

lumen The kidneys showed a moderate grade of interstitial nephritis, both being small, with adherent capsules and granular surfaces The left adrenal gland contained a cortical adenoma 2 by 1 cm in size The uterus was distorted with fibroids The heart was dilated and the muscle flabby Some of the lymph-

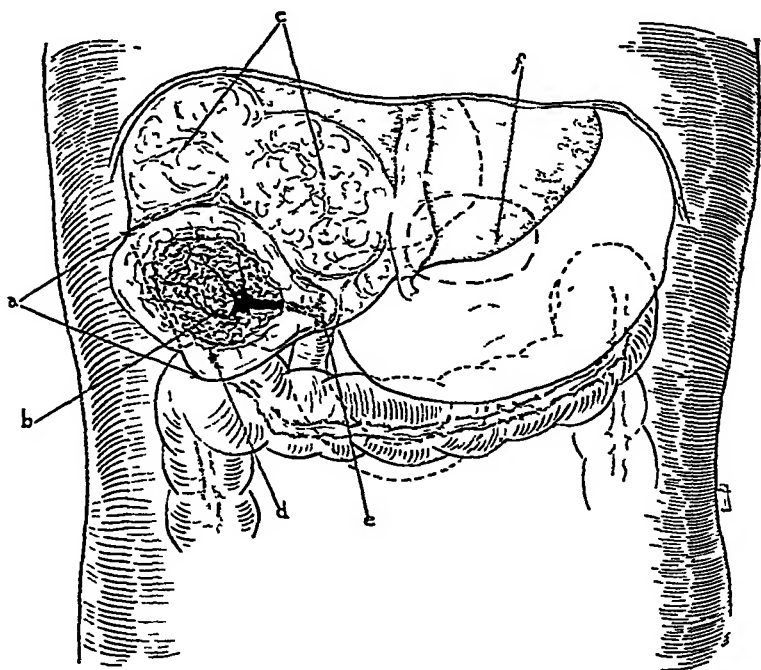


Fig 231 —Diagram of the relation of the carcinoma of the gall-bladder to the duodenum and hepatic flexure of the colon Case I *a*, Primary carcinoma of gall-bladder, *b*, lumen of gall-bladder, *c*, secondary tumor nodules in liver, *d*, perforation in hepatic flexure of colon *e*, perforation in duodenum, *f*, liver metastasis overhanging stomach and felt before death

nodes about the hilum of the liver were enlarged and the seat of metastases It is evident that the primary tumor arose in the gall-bladder with large metastases to the liver and adjacent lymph-nodes and direct extension and perforation into the colon and the duodenum (Fig 231)

The microscopic examination showed the tumor to be an

abdomen began to enlarge rapidly and 170 ounces of a clear straw-colored fluid were removed. The ascites played a very prominent part in the history of this man. The fluid had to be removed every five to ten days in order to keep the man comfortable, 160 to 200 ounces being removed at each paracentesis. The patient gave a history of being a hard drinker. Following removal of the fluid the liver was found to be very much enlarged. The blood examination showed only a slight secondary anemia. There was severe pain in the abdomen, which often extended to the chest and between the shoulders. This pain was particularly marked shortly before the patient's death. There was considerable loss of weight. There was no jaundice. No abdominal masses could be palpated. Other physical examinations and laboratory examinations were negative. A clinical diagnosis of atrophic cirrhosis was made, but syphilis was also suspected. The most striking finding was the enlarged liver and the marked ascites. An abdominal neoplasm was also considered, but later ruled out because of the absence of a localized mass.

The autopsy showed a somewhat enlarged heart with numerous vegetations on the aortic valve. The spleen was enlarged and showed many infarcts. It was covered with adhesions. The lungs showed a hypostatic congestion. The gastrointestinal tract was entirely negative. The main lesions of interest, however, were those associated with the liver. This organ was very markedly enlarged, particularly the right lobe, where there was a yellowish gelatinous tumor mass almost entirely replacing the entire right side of the liver. There were a few small secondary nodules of tumor tissue in other portions of the liver. Some of the lymph-glands at the hilum were also enlarged and filled with the same gelatinous like tumor tissue. The peritoneal cavity contained a large quantity of a slightly blood tinged fluid. The surface of the liver was fairly smooth and its general form and outline was not changed.

Microscopic examination of the tumor tissue shows that it is composed of a wild irregular growth of columnar cells that in places resemble the bile duct epithelium. All of the usual

histologic characteristics of the malignant growth, such as invasiveness, cell variation, wild appearance and architecture, and numerous mitotic figures, are seen throughout the tissue. A very striking secondary change is the marked tendency of these cells to show a mucoid degeneration giving rise to a gelatinous appearance which is noted in the gross.

Primary malignant neoplasms of the liver are relatively uncommon. Secondary neoplasms are much more frequent, being about twenty times as frequent as the primary type. Orth¹ found 4 cases of primary carcinoma of the liver out of 258 cases of malignant tumors in the liver. In other words, most carcinomata of the liver are secondary to some other tumor. They are more frequent in men than in women. Most of them occur between the ages of fifty and seventy. The primary tumor may be derived from two different types of cells, either from the parenchyma cells or the bile-duct epithelium. In our experience the latter has been more frequent. The relative frequency of these two, however, seems to be open to question in the study of the literature. Our case belongs to the biliary type which forms a large massive growth at one side with a few scattered nodules in the rest of the liver. This type of growth does not usually metastasize into other organs, though they do extend into the adjacent lymph-nodes occasionally. They grow rapidly and cause marked enlargement of the liver. Occasionally one shows a tendency to undergo mucoid or gelatinous transformation such as occurred in this case.

The diagnosis of a primary carcinoma of the liver is often very difficult and it is rare that a positive clinical diagnosis can be justified. The progressive enlargement of the liver associated with increasing weakness, loss of weight, cachexia and anemia should always lead to a suspicion of a malignant tumor in the liver. However, it does not necessarily indicate a primary neoplasm of the liver. Oftentimes this enlargement of the liver is associated with pain radiating to the back and to the shoulder. This, in the absence of any other evidence of a primary growth occurring elsewhere, may justify a suspicion of a primary carcinoma of the liver. It is well to note that the pain that occurs

in these cases extends to the back and shoulders and occurs only if the capsule of the liver is stretched and tugged, and is, therefore, a referred pain. If the tumor tissue should press upon the portal vessels, marked ascites would appear in the clinical course of the disease. On the other hand, if the tumor tissue should press more upon the bile-ducts, jaundice would become a prominent symptom. The course of disease is usually very rapid as soon as the ascites and jaundice appear, death occurring usually in four to six months. In this case the severe pain, the rapidly developing cachexia, and the unusually rapid development of ascites are symptoms which indicate that the condition is more than a simple cirrhosis and should suggest a malignancy of the liver. A febrile reaction is not uncommon. This occurred in the present case. Occasionally carcinoma has been found in the liver accidentally in association with an entirely different pathology. The typical course of a primary carcinoma of the liver would be as follows. At first there is a period when there is lack of appetite for fats and meats, with a tendency to lose weight. The patient soon develops a characteristic sallow complexion and a dry skin and begins to complain of abdominal pressure and a sense of fulness in the right upper quadrant. Soon an ache appears in the epigastrium radiating to the right shoulder frequently. Then the liver becomes large and later sensitive. Jaundice or ascites and occasionally both develop, and death soon supervenes.

Case III Multiple Carcinomata of the Intrahepatic Bile-ducts (Malignant Cirrhosis)—This patient was an old lady seventy-three years of age. She had always been in good health until ten weeks ago, when she first noticed a discomfort and pain in the upper right quadrant. Shortly after this she felt a sensation of weight in this region. Two weeks later jaundice appeared and gradually deepened until her death. Following the appearance of jaundice she noticed that her stools were unusually pale and pasty. There was no history of biliary colic. The appetite was poor. There was no vomiting.

Physical examination showed a very intense jaundice, con-

siderable emaciation, and a liver that extended 7 inches below the costal margin. The liver seemed to feel smooth and hard on its surface. It was tender on palpation. There was no ascites. There was some loss of weight. A clinical diagnosis was doubtful, but because of the large liver and intense jaundice a diagnosis of hypertrophic cirrhosis was made.

With exception of the liver the autopsy findings were practically negative. The gall-bladder was normal. There were no gall-stones. The common duct seemed to be normal. The pancreas was normal and showed no tumor nodules. There was nothing extrahepatic to cause the biliary obstruction. The body, generally, however, showed a very intense bile pigmentation. This affected all of the viscera as well as the skin. The liver was especially peculiar. Besides being markedly enlarged, its surface was slightly roughened and it showed a very intense bile pigmentation. It cut with a great deal of resistance and evidently there was a marked increase in fibrous tissue throughout. The cut surface suggested a very marked diffuse cirrhosis. It tended to be more marked in the portal spaces than elsewhere.

Histologic study revealed a very striking picture. There was a patchy fibrosis about the portal spaces. In this location there was considerable proliferation of the bile-ducts, with the development in many places of irregular wild malignant appearing epithelial tissue invading the surrounding structures and very evidently derived from the bile-duct epithelium. The diffuse character of this malignant process with its restriction largely to the bile-duct areas is very striking. The third striking change is the advanced biliary stasis, the bile canaliculi and capillaries being widely distended with plugs of bile and the liver cells containing much fine brown pigment.

This case represents a very unusual type of primary carcinoma of the liver. There is a diffuse neoplastic process affecting most of the small ducts of the liver, leading to very marked fibrosis and irregular epithelial hyperplasia associated with very intense jaundice. There is considerable difference of opinion as to the exact nature of this type of growth. Evidently this epi-

thelial growth is derived from the bile-ducts. There are other cases in which the tumors seem to be derived from the hepatic epithelium. The uniform enlargement of the entire liver with its intense jaundice represents the characteristic features of this growth. Instead of having a single primary focus for the epithelial growth the tumor tissue seems to be multicentric in origin arising from foci scattered throughout the entire liver. It shows a marked tendency to cicatricial fibrosis. It does not metastasize readily outside of the liver, though the portal and mediastinal lymph-nodes may be involved.

A condition such as this could not be diagnosed clinically, yet it may be suspected. It is usually preceded by a large cirrhotic liver and is for that reason often called a carcinomatous cirrhosis. The symptoms are often indefinite. There is a loss of appetite, flatulence, and intense persistent jaundice, with a very large and usually insensitive liver. It is usually associated with the typical cachexia of a malignancy.

Case IV Primary Carcinoma at the Juncture of the Right and Left Hepatic Ducts—This patient was a man aged fifty-one, who complained of jaundice and weakness. He was always well until eleven months ago, when he had frequent stools which were unusually light in color. He often had six to ten stools a day. This was associated with griping pains relieved by bowel movement. At one time he had a diarrhea and fever every day for two months. During the past month the diarrhea still persisted, but was not so severe, having two to four movements a day. Jaundice came on three weeks after the onset of the diarrhea and has gradually deepened. At present there is no abdominal pain. In the last two months there has been increasing weakness and shortness of breath on exertion. There has also been some swelling of the ankles in addition to gradual enlargement of the abdomen.

The physical examination showed an intensely jaundiced, emaciated man. The abdomen was enlarged and fluctuating dulness could be elicited, indicating the presence of fluid. The feet were also swollen. The liver was enlarged, the right lobe

being easily felt and extending to the level of the umbilicus. The left lobe extended some distance below the umbilicus. The urine showed a considerable amount of bile, but was otherwise negative. The stools were clay colored. x-Ray examination of the stomach was negative. It also showed no change in the large intestine. A few days before death the urine showed a considerable amount of sugar.

The clinical diagnosis was left in doubt. A carcinoma at the head of the pancreas was one of the possibilities considered.

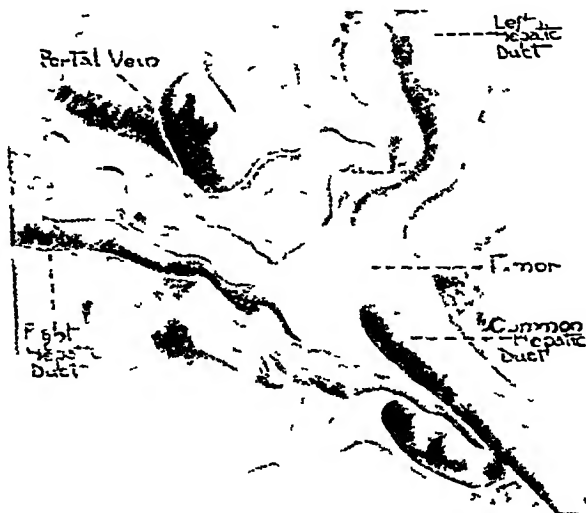


Fig. 232 —Drawing of tumor at the juncture of the right and left hepatic ducts in Case IV.

The presence of a considerable amount of sugar in the urine, the very intense pigmentation (which seemed to be different than the usual type of jaundice), and a large hard liver suggested strongly the possibility of a hemochromatosis. Furthermore a biliary obstruction of some kind was considered but there was no history of biliary colic nor was there any liver tenderness. The gall-bladder could not be palpated. There has been no history of gall-stones. There was marked anemia. The hemoglobin was 37 per cent and the red count was 3,220,000. The

white count 6000. The patient's weakness gradually became more marked, he became drowsy, and soon passed into coma. The day before he died an exploratory laparotomy was performed, and considerable blood-tinged ascitic fluid was found, but no tumor masses could be palpated. The liver was very markedly enlarged, smooth, firm, and intensely jaundiced. The gall-bladder was small and atrophic. No stones were found in the gall-bladder nor in the common ducts. The pancreas did not seem to be enlarged. The patient died the following day.

Unfortunately only a partial autopsy was permitted and a complete examination was not possible. However, the abdominal incision was widened and some interesting findings were noted. There was a considerable blood-tinged fluid. The liver was very large, but its surface smooth. The gall-bladder was only half of its usual size and felt soft and flaccid. There were no stones either in the gall-bladder or in the common ducts. There was no induration about the head of the pancreas or around it. The stomach and intestines showed nothing abnormal besides the pigmentation. The structures about the hilum of the liver were of particular interest. The common duct and the cystic duct appeared normal except along the side of the neck of the gall-bladder and cystic duct, where there seemed to be some indurated fibrous tissue. The side of the common duct felt thickened and indurated. The portal lymph-nodes were enlarged and hard. These nodes showed on section some hard opaque areas suggesting a metastasis. In addition, close to the liver the hilum tissue feels unusually hard and indurated, suggesting a scirrhous growth. On careful dissection the cystic and common duct appeared to be normal. However, there was a small indurated tumor mass into which both the right and the left hepatic duct entered. Above this tumor mass both of these hepatic ducts showed a very marked dilatation which extended well into the liver substance. Some of the main ducts in the liver were 1 cm. in diameter. The ducts below this mass were normal. The gall-bladder was shrunken and contained considerable thick mucus.

Microscopic examination of the indurated tissue showed it

to be composed of very dense fibrous tissue containing larger and smaller cords of epithelial cells with scattered infiltrating acinar-like structures, very irregular in size and shape, and leaving no doubt as to the malignant character of this growth. Some of these epithelial cells showed a tendency to gland formation and were made up of columnar epithelium resembling bile-duct epithelium. Similar epithelium cells and glands with marked fibrosis could be seen in some of the enlarged lymph-glands. No other tumor tissue could be found. In other words, we have here a primary carcinoma arising in the bifurcation of the hepatic duct and causing complete biliary obstruction and intense jaundice.

Tumors arising from the extrahepatic ducts are very uncommon and mostly affect the common duct. They usually arise at the juncture of the cystic and common duct and at the ampulla. The third point of localization is at the juncture of the right and left hepatic duct. Rolleston collected 90 cases, 23 arising at the lower end of the duct, 27 at the juncture of the cystic, hepatic, and common duct, and 19 in the hepatic duct. While in the gall-bladder carcinoma occurs much more frequently in women, in the duct it is more common in men and occurs in late adult life. There is a history of gall-stones in about one-third of the cases. The tumor structure is apt to be scirrhous in type, though the cells here and there tend to form glands which are lined by columnar epithelial cells. There is a marked tendency for the formation of cicatricial fibrous tissue infiltrated with cords of epithelial cells. These tumors never become very large. They tend to infiltrate and thicken the wall of the ducts and do not metastasize widely, though some of the adjacent lymph-nodes may be involved, as in the fourth case. Often there is an annular collar about the duct completely occluding the lumen and causing marked dilatation of the ducts above while the ducts below are normal. These cases are so uncommon that a clinical diagnosis is very rare. The clinical picture is not especially characteristic. A stone in the common duct or a carcinoma at the head of the pancreas may present very similar symptoms. The striking clinical findings

are the intense jaundice, the absence of pain, the progressive emaciation, the clay-colored stools, and also the enlarged liver. The usual symptoms of malignancy are not so prominent because the tumor is relatively small, and it is the mechanical effect of its strategic location that causes the damming back of bile and all the symptoms associated with the obstructive jaundice, these usually coming on before the tumor has become large enough to produce marked cachexia. Ascites occasionally occurs as in this case because of the compression of the portal vessels by the cicatricial tumor tissue in the hilum of the liver. This tumor was placed in the bifurcation of the hepatic duct, a very unusual location, and it is for this reason that the gall-bladder was not distended. Many of the patients give a history of gall-stones or gall-bladder disease preceding the onset of the obstructive symptoms. This occurred in 11 of 20 cases recently reported from the Mayo Clinic. Twelve of them had more or less severe pain, often radiating to the back and the shoulders. Jaundice and intense itching was constant in all of these cases. Clay-colored stools were more frequent. Seven cases gave a history of febrile attacks such as this case under discussion.

Case V. Primary Carcinoma at the Junction of the Cystic, Hepatic, and Common Ducts.—This patient was a woman sixty-six years of age who entered the hospital with marked jaundice, itching, and pain in the epigastrium. She had always been in good health until five months before, when she had a general aching and bilious spell, followed in a few days by jaundice and itching, both of which have persisted throughout the illness. She had difficulty in eating because of the bloating, belching, and burning sensation after taking a meal. With coarse food she often vomited. During the past four weeks she ate nothing but milk and crackers, which gave her the least gastric distress. Shortly after the jaundice began she noted a constant dull aching pain in the epigastrium. She said she had lost considerable weight. She never had previous attacks of jaundice.

Physical examination on admission showed a fairly well-nourished old lady with marked jaundice. There was a staphy-

loma of the right eye The chest was asymmetric, the abdomen rather full, with a lower liver dulness extending 12 cm below the costal margin In the upper right quadrant there was a fat-like mass suggesting an enlarged gall-bladder The spleen was not felt The pulse was 96 to 100 The blood-pressure 120/80 The urine was negative except for the presence of considerable bile The gastric analysis was practically normal, though there seemed to be some retention The red cell count was 4,290,000, the hemoglobin 60 per cent, and the white count 11,500 The x-ray diagnosis of the stomach was a greatly distended gall-bladder and a partial stenosis of the pylorus due to adhesions to the gall-bladder While in the hospital her condition became progressively worse Her weakness and gastric distress increased She became increasingly anemic Three weeks after her first blood-count was made the red count fell to 3,500,000, the hemoglobin to 40 per cent The white count was considerably increased, being as high as 25,000 shortly before her death She had several attacks of epistaxis which were difficult to control Her clotting time was considerably prolonged and, because of the danger of hemorrhage, an exploratory laparotomy was not considered justifiable For several days there was involuntary defecation and micturition and a Cheyne-Stokes' type of breathing followed by death one month after entering the hospital

The clinical diagnosis was considerably in doubt All who examined the patient concurred in the diagnosis of a malignant abdominal disease, but there was some difference of opinion as to the source of the malignancy The final conclusion was that there was a primary growth in the gall-bladder with metastases to the liver, the diagnosis of a primary growth in the stomach being excluded on the basis that the x-ray findings were negative and the gastric analysis did not justify a suspicion of a malignant tumor Carcinoma of the head of the pancreas could not be excluded, especially in view of the absence of a careful stool examination (large copious fatty stools would indicate a disease of the pancreas), nor could a primary carcinoma of the liver be excluded This was a type of case in which the diagnosis

cannot be established except by operation or at autopsy, as there are no means of positive differentiation.

The autopsy findings were of no special interest except for the lesions associated with the liver and biliary tracts and changes indirectly produced by them. All of the tissues showed intense bile pigmentation, especially was this true of the kidneys. There was a staphyloma of one eye. Both kidneys showed a beginning chronic nephritis. There was a moderate arteriosclerosis. Petechial hemorrhages in the skin were unusually

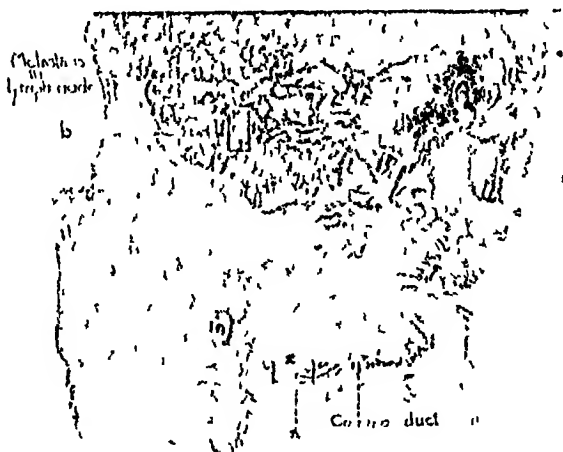


Fig. 233 —Drawing through a section of the primary tumor showing the involvement of the common duct and the mucoid change in adjacent metastatic lymph node. *a* and *b*, Areas from which microphotographs of Case V in Fig. 236 were taken.

numerous, and some were also present in the sclera of both eyes. The pancreas was normal and there was no tumor tissue at the head, nor was there any tumor tissue found directly in the liver substance proper. The stomach and the intestinal tract were entirely normal. The heart was dilated and the muscles quite flabby.

The gall-bladder was very markedly enlarged, extending 5 to 6 cm. below the edge of the liver and measuring 14 cm. in length and 4½ cm. in diameter. It was filled with stones, faceted in type, one of which, measuring 1½ cm. in diameter was firmly

encysted in the cystic duct near the neck of the gall-bladder. Between the stones there was a considerable amount of thick, viscid, pale mucous bile. No bile could be expressed into the duodenum, there apparently being complete obstruction of the cystic duct. About the hilum of the liver and extending along the structures passing through the duodenum there was abundant indurated fibrous tissue particularly marked at the juncture of the cystic duct with the common duct. Both hepatic ducts were dilated and became sharply constricted near the mass of cellular fibrous tissue about the juncture of the cystic duct with the common duct. The portion of the common duct adjacent to the duodenum and the pancreas appeared normal, but the upper end ran into the indurated mass of tissue near the hilum of the liver. This mass of indurated tissue did not measure more than 1 cm. in diameter and 2 to 3 cm. in length. It was not sharply outlined. The hepatic ducts above and the common ducts from below were lost in it. The cystic ducts also entered into this indurated mass of tissue. At one side of this there was an enlarged lymph-gland measuring about 1 cm. in diameter, which on section was made up mostly of a gelatinous-like tissue suggesting a mucoid carcinoma or a metastases of a mucoid carcinoma. There were a few other smaller indurated lymph-glands with the same kind of colloid material within them. No primary tumor tissue could be found in any other location. The liver itself was considerably enlarged, weighing 1900 grams, and showed a typical biliary cirrhosis. The surface of the liver was fairly smooth, but there was some increase in fibrous tissue.

The microscopic study of the slide taken through the indurated tissue about the hilum of the liver showed that it was composed of a scirrhus type of carcinoma completely enclosing the common cystic, and hepatic ducts and their juncture. Irregular gland-like structures could be seen invading the dense fibrous tissue. There was a very marked tendency to fibrosis presenting a typical scirrhus appearance. Some of these glands were enlarged, lined by a single layer of columnar cells resembling bile-duct epithelium and showed a tendency to mucoid de-

generation This mucoid change is especially striking in a metastatic lymph-node taken near the hilum In other words, the indurated tissue evidently represents a primary tumor arising at the juncture of the cystic, hepatic, and common ducts

This case closely resembles both clinically and anatomically the preceding case, but there was one striking difference Because of the lower location of the primary tumor the cystic duct was also occluded and the gall-bladder was markedly dilated Furthermore, it was filled with stones, none of which were found in the fourth case (Usually a gall-bladder filled with stones is contracted) Both cases ran a rapid course, though this case was much more rapid than the preceding one Furthermore, this case was one in which there were numerous stones, although there was no definite history of gall-stone disease The preceding case, however, showed some portal obstruction, there being considerable ascites This was absent in the last case

It is interesting to note that this particular patient had a gall-bladder which was markedly distended and filled with stones and yet she did not give a history of a typical biliary colic, which, as a rule, is usually noted in 50 per cent of the cases Some authors hold that the irritation of gall-stones passing down the bile-ducts is responsible for the development of the neoplastic growth They maintain that the absence of the stones simply means that the stones have passed out into the intestine This, however, does not explain the tumor arising above the cystic duct, as in our fourth case

Case VI Carcinoma of the Ampulla of Vater—This patient, a woman aged seventy, entered the hospital with a complaint of pain to the right of the epigastrium It was spasmodic in character It was first noticed twenty-five years ago, when it lasted all night and was called acute indigestion by her doctor At first these attacks were three or four months apart and lasted three hours at a time, but gradually they became more frequent and severe until in the past two years they have occurred once or twice or more times a week There was no jaundice, no

vomiting until two years ago. The jaundice has been present for the past six weeks. Often the pain radiates to the right shoulder and back. Four years ago the patient was operated upon for gall-stones and the gall-bladder drained. Of late the pain has been unusually severe, being associated with a chill and marked nausea and vomiting. The last severe attack was a week before entering the hospital. This patient has had 6 children, also had a history suggestive of typhoid fever.

Physical examination showed a poorly nourished elderly woman who appeared somewhat jaundiced. The examination of the chest was negative. The liver could be readily palpated. There was an old cholecystotomy scar in the upper right quadrant. There was no tenderness over the liver except immediately following an attack of biliary colic. The stools were pale and clay colored. The blood-count was normal. The blood-pressure also was normal. The Wassermann reaction was negative. There was some tenderness over the gall-bladder region. The clinical diagnosis was a stone in the common duct and the patient was transferred to the surgical service for operation. At the operation the gall-bladder was found covered with adhesions. The right kidney was displaced upward and outward. The common duct was dilated as large as a thumb. It contained a stone 2 cm in length and 1 cm in diameter. This stone was removed and also the gall-bladder. The patient left the operating-room in good condition. The gall-bladder removed showed a thickened wall and a scarred area near its distal end. It did not seem to be very markedly dilated. It contained several small stones and normal appearing bile.

The day after the operation the patient complained of increasing pain in the upper abdomen. Her pulse became weak and rapid. The gauze drain was removed and a large amount of bile-stained fluid drained out through the opening. The temperature became elevated to 102° F. Her condition rapidly became worse and death followed the next day.

At autopsy there seemed to be some jaundice but this was not marked. The abdomen appeared distended. The peritoneal surfaces appeared dull and the pelvis contained bile-stained pus.

A purulent exudate was present in the upper right quadrant. There were numerous peritoneal adhesions, particularly over the right upper quadrant. There were also adhesions over the pleura of both lungs and over the spleen. The pancreas was small, but otherwise normal. The kidneys were also small with a granular surface and adherent capsule, typical of a chronic

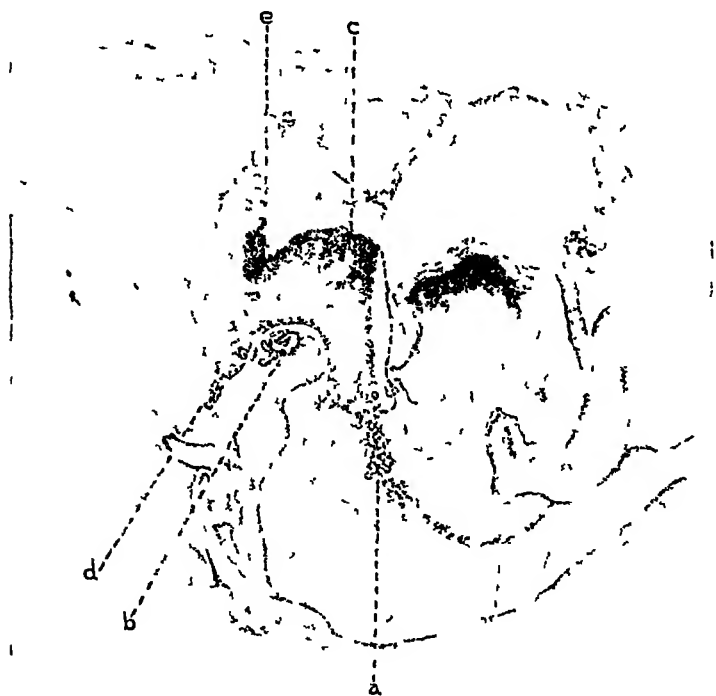


Fig. 234 —Drawing of carcinoma of ampulla of Vater and dilated common and hepatic ducts. Case VI. *a*, Carcinoma of ampulla, *b*, ligature about stump of cystic duct, *c*, dilated common duct, *d*, dilated left hepatic duct, *e*, dilated right hepatic duct.

nephritis. The right kidney possessed two distinct pelvises and ureters, which united near their opening in the bladder. Anomalous arteries entered the lower pole of each kidney. The aorta showed a moderate grade of arteriosclerosis. There was a fetal adenoma in the thyroid gland. The most prominent lesion, however, was that involving the liver and biliary tract. The

liver was about normal in size and showed surprisingly little bile-pigment. The surface was roughened and it presented the typical appearance of a biliary cirrhosis. The hepatic duct showed marked dilatation. The most striking change, however, affected the common bile and hepatic ducts. Beneath the hilum the common duct appeared like a thick distended tube $2\frac{1}{2}$ cm in diameter. Its circumference was $5\frac{1}{2}$ cm. On pressure a small amount of bile could be expressed between two of the sutures, one of which had partially given away. As it was, the duct was tense and looked more like a tense displaced gall-bladder. No bile could be expressed into the duodenum. This opening between the sutures was probably the source of the bile-stained exudate in the peritoneal cavity. This common duct was markedly dilated and the dilatation extended well up into the branches of the hepatic duct in the liver. The wall seemed to be markedly thickened. This dilatation of the duct extended down to within 1 cm of the opening of the duodenum. At this place there seemed to be a rather friable, dense indurated tissue, suggesting a carcinoma or tumor arising in the ampulla of Vater. This indurated mass was not more than 6 to 8 mm in diameter and 12 mm in length. Bile could not be expressed into the duodenum. The liver did not seem to show a very striking amount of bile pigmentation which would have been suspected (Fig 234).

The histologic examination showed a typical biliary cirrhosis of the liver with marked thickening of the wall of the bile-ducts, particularly of the common duct and an adenomatous mass of tissue situated about the ampulla of Vater. This adenomatous mass showed a considerable irregular growth of the epithelium suggesting a beginning malignant change. In other words, there is here an early carcinoma of the ampulla of Vater which has completely obstructed the common duct, and explains why the stitches made in the side of the common duct finally gave way and allowed bile to discharge into the peritoneal cavity.

The smears and cultures of the peritoneal exudate showed no organisms.

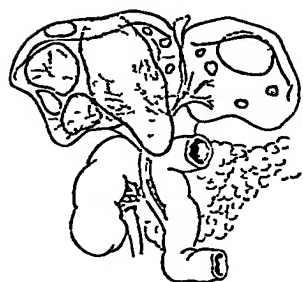
Tumors in the region of the ampulla are not uncommon, but their origin, except in very early cases, is difficult to ascertain because they may arise from the cylindric epithelium of the common duct as most of them do, from the mucous glands of the duodenum, and from the pancreas. These tumors are usually small, but whatever their origin, they tend to increase the stenosis with dilatation of both the gall-bladder and common duct. In our case it is rather unusual that the gall-bladder was not particularly distended in comparison with the marked distention of the common duct. These tumors of the common duct, both of the ampulla and elsewhere, declare themselves early, hence encourage surgical interference. The results of operations, however, are not very encouraging.

The symptoms cannot be distinguished readily from a common duct stone or a carcinoma at the head of the pancreas, though the latter might give a different appearing stool. The stone in this case probably contributed to the jaundice and probably also stimulated the growth in the ampulla. The jaundice in this type of case is more intermittent at first and later becomes persistent. The liver is usually enlarged. The tumors are so small that rarely can they be palpated. They may be distinguished from stones, in that the obstruction is more complete and the stools are not apt to show bile. Febrile reactions in cases of this kind are common.

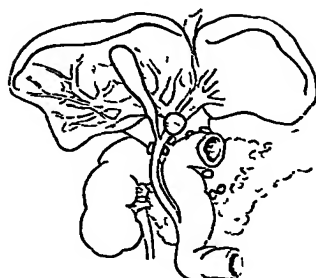
This patient showed one complication that is common with Case V, that is, the tendency to marked hemorrhage, which is probably the result of the damming back of bile, causing an altered coagulability of the blood.

The absence of marked bile pigmentation of the liver with other evidences of marked biliary obstruction is unusually interesting. It may be due to the fact that following the operation the bile was drained away, leaving only histologic evidences of pigmentation and a large distended duct (Fig. 235).

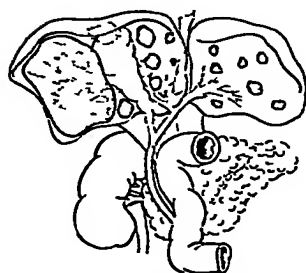
These 6 cases present many points in common, some of which are of special interest. All are examples of malignant growths derived from the columnar epithelial lining of the bile-ducts, but arising in different locations and presenting various



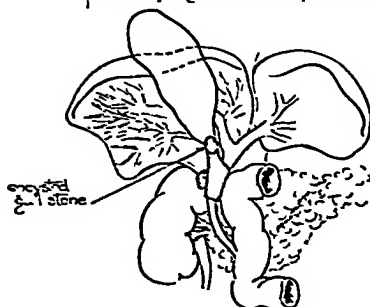
Case I—Primary carcinoma of gall bladder



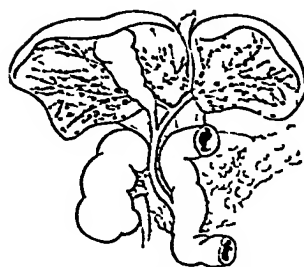
Case II—Primary carcinoma at junction of right and left hepatic ducts



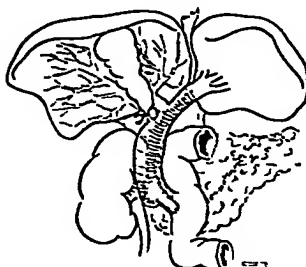
Case III—Primary carcinoma of liver



Case IV—Primary carcinoma at junction of cystic and common bile ducts



Case V—Multiple carcinoma of intrahepatic bile ducts



Case VI—Carcinoma of ampulla of Vater

Fig 235.—Diagrams illustrating the location and relations of the tumors in the six different cases reported. The shaded areas represent the tumor tissue.

clinical pictures. While in all 6 cases there was more or less marked cachexia of a malignant disease, it was only in the first

case that death can be said to be due to the cachexia, though complications played a larger rôle than suspected. In all the other cases the complications considerably shortened the course of the disease. In the second case it was the vegetative lesions in the heart valves and the handicap of a rapidly developing ascites from portal obstruction that shortened the duration of the disease. In the last case it was the peritonitis following the removal of a stone in the common duct that brought about an unexpected end to the disease. The other 3 cases possessed the same complication, namely, the toxic results of biliary obstruction, which greatly overshadowed the symptoms of a malignancy and terminated the disease before the latter was markedly manifested. Because of the mechanical effects resulting from the strategic location of these tumors they never become very extensive or large.

It is noteworthy that the course of the disease is rapid in all of these cases, with the possible exception of the last one reported. Two of the cases ran their course in little over three months. Four of the cases were in women all of whom were past the age of sixty (Fig 236).

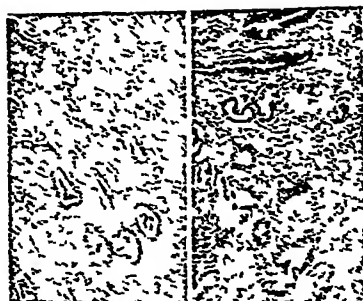
The relation of these cases to gall-stones is unusual. In only 2 cases were there gall-stones and in 1 of these 2 there were no symptoms of biliary colic or stones. The relationship to stones is usually higher.

A large, distended, palpable gall-bladder associated with increasing persistent jaundice, in the absence of a history of gall-stones, strongly suggests a malignant obstruction of the biliary excretory duct, such as either a carcinoma of the biliary passages or of the head of the pancreas. Increasing weakness, loss of weight, and cachexia make malignancy still more probable.

In these cases one symptom was present in some form, that is, some type of epigastric distress, such as a weighty feeling in the upper right quadrant, a dull ache, sharp colicky pains, tenderness, or some combination of them. Jaundice was the next most characteristic finding, being present in the last 4 cases.



Case I



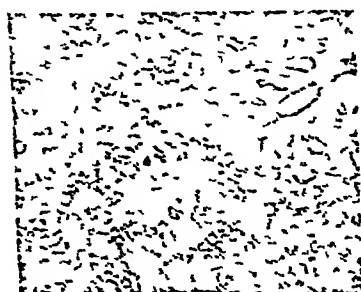
Case II



Case III



Case IV



Case V



Case VI

Fig. 236.—Photomicrographs illustrating the appearance of the tumor tissue of the different cases. In Cases IV and V the primary tumor is to the left and the metastasis in the lymph nodes to the right.

One of the cases (V) showed considerable sugar in the urine. Glycosuria is occasionally reported in carcinomata of the ex-

trahepatic bile-passages Histologic examination of the pancreas showed some atrophy of the islands of Langerhans and a chronic pancreatitis, but no relation could be established with a malignancy, unless it be that the toxic action of retained bile caused degenerative changes in the pancreas

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MALFORMATION OF THE ADRENAL GLANDS WITH THE CLINICAL PICTURE OF ADDISON'S DISEASE

THE patient was a married woman aged forty-six, whose illness began nineteen years ago with what she called an early menopause. Her physician told her then that her trouble was due to an early cessation of menstruation. Since then she never had been entirely well and had had frequent attacks of sore throat and bronchitis. She had also been troubled with dyspepsia and diarrhea. From the history available it is difficult to state when symptoms suggestive of Addison's disease began. Sixteen months before her death she successfully passed a physical examination for life insurance. No note of her blood-pressure was made at this time. Five months before her death she showed more marked symptoms, felt very much worse, there were marked weakness, considerable diarrhea, and a rapid loss of weight. The skin had become "copper spotted," especially in the palms of the hands. The only blood-pressure reading noted in her history was one made five weeks before death when a systolic pressure of 60 was recorded, while the diastolic pressure was only 40 to 42.

A clinical diagnosis of Addison's disease was made. At autopsy comparatively few findings were noted, though tuberculosis is most frequently found in the adrenal glands, usually associated with tuberculosis elsewhere. No evidence of this condition was found. The only striking lesion present was a pair of unusually small but otherwise apparently normal suprarenal glands.

The left adrenal gland weighed only $2\frac{1}{2}$ grams as compared with the normal adult weight of 5 to 6 grams. This adrenal measured about 25 by 15 by 2 to 3 mm. The fatty tissue about it was very abundant and could be readily removed. The organ was unusually firm in consistency. It had a deeper brown color than is usual. The cut surface was peculiar in that it

seemed to be composed of pale brown cortical tissue with no recognizable medulla (Fig 237)

The histologic picture is very unusual, but quite characteristic. The first impression is that it consists of lymphadenoid tissue rather than suprarenal tissue. Neither cortex nor medulla can be easily recognized. Here and there small clumps of epithelial cells may be seen surrounded by lymphoid-like cells. These probably were cortical in origin. The tissue is very cellular, most of the cells being small mononuclear cells resembling but



Fig 237 —Drawing of cross-section through the gland (enlarged 5x)

not identical with lymphocytes. These small cells are often massed in clumps with larger cells in the center suggesting lymphoid follicles. There are some epithelial cells arranged in an irregular reticulum suggesting medullary tissue. The capsule about the gland is unusually heavy, thick, and dense. The small deep staining cells are often in masses just underneath this capsule. Extending from the capsule there is a wide-meshed, coarse reticulum which often contains many very large dilated capillaries. Within this reticulum there are large masses of small dark staining cells above described. Many of these

small round cells do not show a definite cytoplasmic outline. They appear as numerous deep staining nuclei embedded in a fibrillar syncytium. Aside of some scattered cuboidal cells suggesting a portion of the cortical layer there is no evidence of the cortex present. The capsule seems to rest directly upon the medulla which is heavily infiltrated with numerous round cells. The striking characteristic of the section is that in spite of the large numbers of these small deep staining cells there is no definite inflammatory reaction and there is nothing to suggest tuberculosis or syphilis, nor does the change that is present appear like a simple cirrhosis or a simple atrophy (Fig 238)

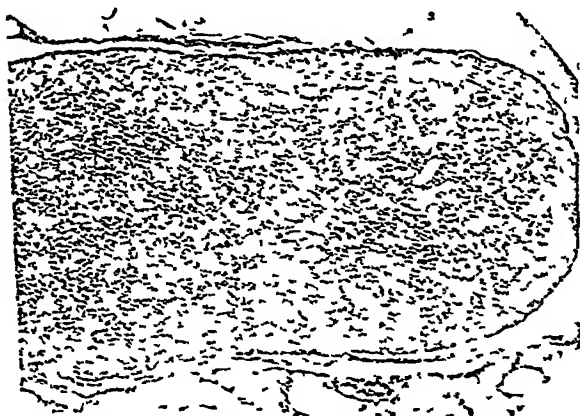


Fig 238 —Microphotograph through end of adrenal gland

While the above lesion is uncommon in Addison's disease it has been described repeatedly. It is not nearly as common as tuberculosis of the adrenal glands and has been regarded as an atrophic process. It should not be confused with the simple atrophy of the adrenal gland because this process evidently is quite of a different nature. However, Bloch has clearly shown the intimate relation of this condition to the developmental changes occurring in the adrenal gland and considers it merely an abnormal extension of the changes which normally occur in the adrenal gland. It is well known that the cortex has a very

different origin than the medulla, the former arising from the urogenital anlage and the latter from the embryonic sympathetic nervous system. During the fourth and fifth months of fetal life there is an unusual and rather large organ situated between the two kidneys known as the paraganglion. This organ is composed of embryonic neurocytes belonging to the sympathetic nervous system. On each side of this organ there is a small body which is composed of cortical tissue and comprises the adrenal body at this period. Some of the neurocytes in the paraganglion migrate through the capsule and outer portion of the cortex or adrenal gland as it is at that time and accumulate in the center where they eventually differentiate into the mature adrenal medulla. The paraganglion attains its maximum development between the fourth and fifth month, after which it gradually disappears as the sympathetic system and the adrenal medulla becomes more and more developed, so that at birth but few of the neurocytes may be seen. However, frequently in early infancy, some of these undifferentiated cells, appearing as small deep staining mononuclear cells, may still be seen migrating through the cortex of the adrenal gland to the center where they differentiate into the medulla. Migration of these cells is associated with an atrophy of the inner portion of the cortex, that is, the part that is adjacent to the medulla. At the same time there is a regeneration of the glomerular zone of the cortex. Occasionally this process is perverted and prolonged into early childhood and even into later life, when the embryonic cells accumulate in the medulla, show little tendency to differentiate, and at the same time there is more rapid degeneration of the cortex and atrophy of this layer resulting in the anatomic picture just described and in functional insufficiency of the adrenal glands manifested clinically in Addison's disease.

If this theory of Bloch is correct, and I believe that it is in our case, most of the small mononuclear cells described in this section are to be interpreted as embryonic neurocytes. They do resemble cells that are seen in certain malignant tumors derived from the adrenal medulla and known as malignant neuroblastomata. I have seen the same type of cells in the paraganglion of a

four-month-old human fetus. Accordingly, we can consider that the process, which leads to an organ such as we have here, represents a gradual malformation of the adrenal gland, the cortex atrophying almost completely, the medulla enlarging and accumulating many embryonic neurocytes which, however, seem to have lost the power of complete differentiation to a functioning tissue. That the symptoms of Addison's disease did not begin earlier is probably explained by the fact that there was a partial differentiation of these tissues earlier in life. This tissue gradually became exhausted, resulting in a gradual development of an insufficiency of the internal secretion of this gland.

The most common lesion that is found in association with Addison's disease is tuberculosis of the adrenal gland (Lewin, 75 per cent). This condition is usually bilateral and also is usually associated with tuberculosis in other parts of the body. However, about 17 per cent of one series of cases (Elsasser, 549 cases) no tuberculosis was found in any other part of the body. It is perhaps also worth noting that a tuberculous process in the adrenal gland is usually very diffuse with rather extensive masses of caseation. The next frequent lesion is probably syphilis and then a simple atrophy. This simple atrophy should not be confounded with the condition that has just been described. It is perhaps also well to note here that occasionally Addison's disease may be present without any noticeable lesions in the adrenal gland, at least apparently so. In other cases extensive destruction of the suprarenals may occur without the clinical symptoms of Addison's disease. These, of course, are very unusual and are not easily explained.

It is well known that complete removal of the adrenal glands is incompatible with life. Inasmuch as this organ is composed of two entirely distinct tissues differing in origin, in appearance, and in structures, the relative importance of them in Addison's disease has led to a great deal of discussion and difference of opinion. The medulla contains a specific secretion, epinephrin. It has a very definite action, particularly in increasing the tone of the smooth muscles supplied by the sympathetic system,

such as the gastro-intestinal tract and arteries, but this, however, does not imply that the medulla is most essential to life. In fact, where formerly the medulla was considered the more important factor in the pathogenesis of Addison's disease, recent work seems to indicate that the cortex is much more important than the medulla. Bittorf collected 50 cases in which there was marked atrophy of the adrenal glands, and his conclusion was that the medulla was a more important factor than the cortex. Wiesel came to the same conclusion that in Addison's disease the destruction is primarily in the medulla. On the other hand, Scott, Karakascheff, and Lowy feel that the cortex is the primary seat of the destruction. Houssay and Lewis have destroyed the medullary substance in dogs without any marked disturbance. Falta and Meyer feel that the cortex is equally important and that the cortex supplies the substance which the adrenal uses in making epinephrin. After removal of the adrenal glands epinephrin which is the specific secretion of this organ does not remove the symptoms or save the animal. Administration of adrenalin is very unsatisfactory in Addison's disease. Only animals with accessory adrenal glands which are composed of cortical substance withstand the removal of these glands. Furthermore, the removal of the adrenal medulla does not produce the same symptoms as the excision of glands, and Biedl has shown in certain species of fishes in which the cortex and the medulla of the adrenal glands are separate, removal of the cortical portion called the interrenal body causes death within a few days. However, if a small amount of the cortex is left behind death does not occur. Moreover, if the chromaffin tissue in other parts of the body is the functional equivalent to that of the adrenal medulla, as some maintain it is, it is difficult to understand the serious effect in removing only the part in the adrenal glands. In other words, evidence is much more strongly in favor of the idea that the cortex of the adrenal gland is a very important if not the most important factor in the production of the clinical syndrome known as Addison's disease.

The recent physiologic work has thrown a great deal of

doubt upon the importance of the medullary secretion of these glands. There is evidently very little evidence that the epinephrin content of the suprarenal vein is sufficiently increased to produce a marked tonic effect upon the various smooth muscles of the body. In Addison's disease epinephrin is practically absent. It is not easy to explain the various symptoms that occur in Addison's disease. It has been said that the low blood-pressure and general muscular and gastro-intestinal asthenia is due to the absence of epinephrin which is normally secreted by the adrenal medulla. The fact that injection of adrenalin in these patients is often disappointing seems to confirm some of the skepticism regarding the importance of the adrenal secretion which has been brought forth by some of the recent physiologic work. Evidence seems to point more and more to the increasing value of the cortex. The cause of the pigmentation in the patient is not easily explained. One theory is very suggestive, though the links of evidence are not all complete. We know that epinephrin is closely allied to tyrosin. Further, we know that oxidizing ferments readily convert epinephrin, tyrosin, and related aromatic compounds into brown pigments. In addition, we know further that in Addison's disease there is a deficiency in a tissue that is deeply involved in the metabolism of the chromogenic aromatic compounds. Hence the accumulation of aromatic substances, such as tyrosin, in the skin which otherwise would be changed to epinephrin becomes here oxidized and combined into melanin pigments. In this connection it is interesting to note that Bittorf observed that the skin of persons with Addison's disease has an increased power of oxidizing epinephrin and tyrosin to pigmented substances. It is well to note, however, that Addison's disease may occur in the absence of pigmentation.

There is one point in this patient's history which is worthy of further mention, and that is the early appearance of the menopause. This can be readily explained by the complete absence of the cortical tissue, for it is generally accepted that there is a close relationship between the cortex of the adrenal gland and the development of the genital organs. It is quite likely that

with the cessation of menstruation there was a corresponding atrophy of the cortex of the adrenal gland which by the time the patient died has almost entirely disappeared. It has also been noted that patients with this condition, that is Addison's disease, frequently give a long history of more or less general physical debility and lack of resistance many years before the actual symptoms come on, and this fact seems to be duplicated in this particular patient. In fact, there are many who include a condition of status lymphaticus with an enlarged persistent thymus along with this disease. In this particular case, however, no enlarged thymus was noted.

It is also worth noting that in this case the true nature of the disease was not recognized until the peculiar pigmentation of the skin developed. This is very frequently true. The most striking symptoms are those arising from the progressive muscular and gastro-intestinal asthenia without apparent cause and the low blood-pressure. These should always lead to a strong suspicion of Addison's disease. The appearance of the pigment in the palms of the hands is rather unusual. Its appearance in the mucous membranes of the mouth is more characteristic and often aids in differentiating this condition from other pigmentations of the skin in which the mucous membranes are not involved.

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